Clinical and prognostic significance of histamine monitoring in patients with CML during treatment with imatinib (STI571)


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Background: Although imatinib is highly effective in chronic myeloid leukemia (CML), drug-resistance may occur. Therefore, monitoring of minimal residual disease (MRD) during treatment with imatinib is important. However, most MRD-parameters are expensive and require special technology. We determined the value of histamine as MRD-marker in CML.

Patients and methods: Histamine levels were measured serially in whole blood samples before and during imatinib therapy in 80 CML patients by radioimmunossay.

Results: Histamine levels were highly upregulated in CML at diagnosis compared to healthy controls, and correlated with the presence of basophils. During treatment with imatinib, histamine levels decreased and returned to normal levels in those achieving a complete cytogenetic response (CCR). Loss of CCR during therapy was invariably accompanied by an increase in histamine. Moreover, a histamine level of >100 ng/ml three or six months after start of imatinib was associated with a significantly reduced probability of survival (p < 0.05). Whereas basophils were found to correlate well with histamine during imatinib, no correlations were found between histamine and Ph+ metaphases or histamine and BCR/ABL.

Conclusion: Histamine-monitoring during treatment with imatinib is of prognostic significance.

Key words: basophils, CML, histamine, imatinib, MRD

Introduction

Chronic myeloid leukemia (CML) is a neoplasm of hematopoietic progenitors exhibiting the reciprocal translocation t(9;22) [1,2]. The respective oncoprotein, BCR/ABL, is critically involved in the pathogenesis of CML [3,4]. The clinical course in CML is divided into a chronic phase (CML-CP), accelerated phase (CML-AP), and a blast phase (CML-BP) [1]. During CP, the clinical course is indolent. Most patients have a left shift in their differential counts as well as slight to moderate basophilia [2,4,5]. During acceleration, the myeloid compartment undergoes transformation with an increase in immature cells [1,4,5]. In addition, substantial basophilia is seen in most cases [1,4–7]. The terminal phase of CML (BP) resembles acute leukaemia [1,4].

Several effective therapies for CML have been introduced in the past [8–16]. Currently, imatinib is considered standard first-line therapy. This BCR/ABL kinase inhibitor produces major cytogenetic responses (MaCR) in a majority of all patients [11–16]. However, it has also been described that resistance against imatinib can occur [17–19]. Therefore, it is important to predict responses to therapy and to monitor the levels of minimal residual disease (MRD) in these patients [11–16,20–23].

Accepted tests for monitoring MRD in CML are cytogenetics and quantitative BCR/ABL [20–23]. However, such monitoring requires special technology and equipment. Moreover, in many cases, karyotyping does not work because of poor cell-growth. Also, CML patients may develop Ph-negative subclones [23,24].

Histamine is a specific product of basophils and is highly upregulated in CML [25,26]. Most of the histamine in these patients derives from leukemic cells as basophils are clonal in CML [25–27]. Moreover, basophils are an important prognostic variable in CML—patients [5–7]. However, depending on the disease-phase, basophils may be quite immature and thus difficult to identify by morphology [28]. In addition, it is often impossible to quantify basophils during imatinib because of their low frequency. The application of basophil-markers may be helpful in this regard. Of particular interest are markers expressed at all stages of basophilopoiesis such as histamine.

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In this study, we examined the value of histamine as a basophil-specific marker in CML, and asked whether histamine would serve as a prognostic and MRD parameter.

**Patients and methods**

**Patients' characteristics**

Ninety-seven patients with Ph+ CML (females, n = 35; males; n = 62) were examined. Median age at diagnosis was 54 years (range: 19-83). According to established criteria [1] 86 patients had CML-CP, 9 CML-AP, and 2 had myeloid BP at diagnosis. Before blood or bone marrow (BM) examination, written informed consent was obtained. The patients’ characteristics are shown in Table 1A.

**Treatment and evaluation of hematologic response**

Most patients received initial cytoreduction with hydroxyurea. Of the 97 patients, 14 underwent allogeneic (n = 12) or autologous (n = 2) stem cell-transplantation (SCT), either frontline or after therapy with interferon-alpha (IFN-α). Forty-eight of the 97 patients received IFN-α as initial therapy. A total of 36 patients received imatinib without previous therapies (except hydroxyurea). At start of imatinib, 62/80 patients (77.5%) were in CML-CP, and 18 (22.5%) had CML-AP or CML-BP (Table 1B). Initially, patients with CML-CP received imatinib at 400 mg per os daily. Patients who had or developed AP, did not respond adequately to 400 mg/day, or lost complete cytogenetic response (CCR), received 600-800 mg imatinib daily. In select cases, the imatinib-dose was reduced.

Table 1A. Patients’ characteristics - all patients with CML at diagnosis

<table>
<thead>
<tr>
<th>n</th>
<th>f/m ratio</th>
<th>median pb histamine (ng/mL)</th>
<th>median age-yrs</th>
<th>median Hb (g/dL)</th>
<th>median WBC (cells/µL)</th>
<th>median plt/µL</th>
<th>median pb blasts (%)</th>
<th>median pb BA (%)</th>
<th>median pb BA (cells/µL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP</td>
<td>86</td>
<td>1:1.8</td>
<td>4,618</td>
<td>54</td>
<td>11.85</td>
<td>115,100</td>
<td>398,500</td>
<td>5</td>
<td>5,755</td>
</tr>
<tr>
<td>AP/BP</td>
<td>11*</td>
<td>1:1.75</td>
<td>11,242</td>
<td>53</td>
<td>10.3</td>
<td>94,000</td>
<td>383,000</td>
<td>11</td>
<td>10,340</td>
</tr>
<tr>
<td>all pts</td>
<td>97</td>
<td>1:1.8</td>
<td>5,563</td>
<td>54</td>
<td>11.4</td>
<td>110,000</td>
<td>397,000</td>
<td>5</td>
<td>5,500</td>
</tr>
</tbody>
</table>

CP, chronic phase; AP, accelerated phase; BP, blast phase; pb, peripheral blood; yrs, years; WBC, white blood count; BA, basophils; Hb, hemoglobin; plt, platelets; *In the AP/BP group, 9 patients had CML-AP, and 2 patients had CM-BP (myeloid type BP).

Table 1B. Patients’ characteristics – all patients before start of treatment with imatinib

<table>
<thead>
<tr>
<th>n</th>
<th>f/m ratio</th>
<th>median pb histamine (ng/mL)</th>
<th>previous IFN-α (n)</th>
<th>median WBC (cells/µL)</th>
<th>previous SCT (n)</th>
<th>median pb blasts (%)</th>
<th>median pb BA (%)</th>
<th>median pb BA (cells/µL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP</td>
<td>62</td>
<td>1:1.8</td>
<td>1,168</td>
<td>58</td>
<td>33</td>
<td>15,590</td>
<td>02</td>
<td>0</td>
</tr>
<tr>
<td>AP/BP</td>
<td>18*</td>
<td>1:1.25</td>
<td>2,431</td>
<td>57</td>
<td>10</td>
<td>18,870</td>
<td>02</td>
<td>3</td>
</tr>
<tr>
<td>all pts</td>
<td>80</td>
<td>1:1.7</td>
<td>1,185</td>
<td>58</td>
<td>43</td>
<td>16,530</td>
<td>04</td>
<td>0</td>
</tr>
</tbody>
</table>

pb, peripheral blood; yrs, years; WBC, white blood count; BA, basophils; Hb, hemoglobin; plt, platelets; *In the AP/BP group, 16 patients had CML-AP, and 2 patients had CM-BP.

**Figure 1.** Histamine-levels at diagnosis and correlation with blood basophils. Figure 1A shows whole blood histamine-levels at diagnosis in 44 patients with CML (CML-CP, n = 38; CML-AP, n = 4, CML-BP, n = 2), and - for comparison - histamine-levels in 39 age-matched healthy controls. The difference in histamine-levels were statistically significant (p<0.0001). Figure 1B shows the correlation between histamine-levels and the absolute numbers of basophils (per µL blood) in the 44 CML patients at diagnosis (p<0.001).
because of severe cytopenia (n = 6) or hepatotoxicity (n = 1). Part of patients were included in the IRIS-trial [12,13] or ‘post-IRIS-trials’ (n = 39). Response-assessment was performed using generally accepted criteria [12–16].

**monitoring of responses to imatinib by cyto genetics**
The percentage of Ph+ bm metaphases was examined in 3 months-intervals during the first year, and thereafter in 6 months-intervals. Responses to imatinib were classified as proposed [11–16]: CCR: < 1% Ph+ metaphases; partial CR (PaCR): 1-35%; minor CR: 36-65%. A major CR (MaCR) was defined as complete or partial CR (0-35%).

**monitoring of BCR/ABL**
BCR/ABL-levels were determined in blood and bm cells before therapy, and serially during imatinib (pb: 1-3 months-intervals; bm: 3-months-intervals during the first year, thereafter in 6-months-intervals). BCR/ABL was quantified by real time RT-PCR with light cycler-technology using c-ABL as internal reference-gene [20–22]. Results were expressed as percentage of BCR/ABL-transcripts relative to c-ABL. A major molecular response (MMR) was defined as ≥ 3 log-decrease in BCR/ABL.

**measurement of histamine-levels at diagnosis and during therapy**
In 44 patients, blood samples were available at diagnosis for histamine-measurement. For comparison, histamine-levels were also determined in 39 age-matched healthy controls. In all patients receiving imatinib (n = 80), histamine was determined 1-3 times during the first month, and thereafter in 1- to 3-months-intervals. Histamine was quantified in whole blood-samples after cell-lysis (in distilled water plus freeze–thawing) by RIA (Immunotech, Marseille, France) as described [26]. A complete biochemical response (CBR) was defined as decrease of blood histamine to < 100 ng/ml.

**statistical evaluation**
To compare histamine-levels among subgroups of patients and between patients and controls, the Mann-U and Kruskal Wallis tests (multiple groups) were applied. A linear correlation was employed to test

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**Table 2. Hematologic, cytogenetic, molecular, and biochemical response to imatinib**

<table>
<thead>
<tr>
<th>Patients - groups</th>
<th>CHR</th>
<th>CCR</th>
<th>MaCR</th>
<th>MMR (3 log ↓)</th>
<th>CBR (histamine &lt;100 ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>74/80 (92.5%)</td>
<td>46/80 (57.5%)</td>
<td>60/80 (75%)</td>
<td>39/80 (48.8%)</td>
<td>71/80 (88.8%)</td>
</tr>
<tr>
<td>CP all pts</td>
<td>61/62 (98.4%)</td>
<td>40/62 (64.5%)</td>
<td>53/62 (85.5%)</td>
<td>34/62 (54.8%)</td>
<td>58/62 (93.6%)</td>
</tr>
<tr>
<td>AP all pts</td>
<td>12/16 (75.0%)</td>
<td>6/16 (37.5%)</td>
<td>7/16 (43.8%)</td>
<td>5/16 (31.3%)</td>
<td>12/16 (75.0%)</td>
</tr>
<tr>
<td>BP all pts</td>
<td>1/2 (50.0%)</td>
<td>0/2 (0.0%)</td>
<td>0/2 (0.0%)</td>
<td>0/2 (0.0%)</td>
<td>1/2 (50.0%)</td>
</tr>
<tr>
<td>Imatinib I.Th. – all pts</td>
<td>36/36 (100%)</td>
<td>23/36 (63.6%)</td>
<td>28/36 (77.5%)</td>
<td>20/36 (55.6%)</td>
<td>34/36 (94.4%)</td>
</tr>
<tr>
<td>Imatinib I.Th. – CP</td>
<td>29/29 (100%)</td>
<td>21/29 (72.4%)</td>
<td>26/29 (89.6%)</td>
<td>18/29 (62.1%)</td>
<td>28/29 (96.6%)</td>
</tr>
<tr>
<td>Imatinib I.Th. – AP</td>
<td>6/6 (100%)</td>
<td>2/6 (33.3%)</td>
<td>2/6 (33.3%)</td>
<td>2/6 (33.3%)</td>
<td>5/6 (83.3%)</td>
</tr>
<tr>
<td>Imatinib I.Th. – BP</td>
<td>1/1 (100%)</td>
<td>0/1 (0.0%)</td>
<td>0/1 (0.0%)</td>
<td>0/1 (0.0%)</td>
<td>1/1 (100%)</td>
</tr>
<tr>
<td>P.Th. → Imatinib – all pts</td>
<td>38/44 (86.4%)</td>
<td>23/44 (52.3%)</td>
<td>32/44 (72.8%)</td>
<td>19/44 (43.2%)</td>
<td>37/44 (84.1%)</td>
</tr>
<tr>
<td>P.Th. → Imatinib – CP</td>
<td>32/33 (97.0%)</td>
<td>19/33 (57.6%)</td>
<td>27/33 (81.8%)</td>
<td>16/33 (48.5%)</td>
<td>30/33 (90.9%)</td>
</tr>
<tr>
<td>P.Th. → Imatinib – AP</td>
<td>6/10 (60.0%)</td>
<td>4/10 (40.0%)</td>
<td>5/10 (50.0%)</td>
<td>3/10 (30.0%)</td>
<td>7/10 (70.0%)</td>
</tr>
<tr>
<td>P.Th. → Imatinib – BP</td>
<td>0/1 (0.0%)</td>
<td>0/1 (0.0%)</td>
<td>0/1 (0.0%)</td>
<td>0/1 (0.0%)</td>
<td>0/1 (0.0%)</td>
</tr>
</tbody>
</table>

CP, chronic phase; AP, accelerated phase; BP, blast phase; I.Th, initial therapy; P.Th., previous therapy i.e. before start of imatinib; CHR, complete hematologic response; CCR, complete cytogenetic response; MaCR, major cytogenetic response; MMR, complete molecular response (defined by ≥ 3-log decrease in percent BCR/ABL); CBR, complete biochemical response defined by a decrease of whole blood histamine-levels to less than 100 ng/ml. * responses represent the best response obtained within 12 months after start of therapy with imatinib.

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**Figure 2.** BCR/ABL mRNA levels during treatment with imatinib. The figure shows BCR/ABL mRNA levels (relative to c-ABL) during treatment with imatinib in CML patients who entered a complete cytogenetic response, CCR (2A), and BCR/ABL mRNA levels in patients who did not achieve a CCR (2B). BCR/ABL was quantified by light cycler-based real time PCR (see text). Results show minimum and maximum BCR/ABL mRNA levels (bars), the mean (●) and median BCR/ABL levels (―), and 25th and 75th percentile of BCR/ABL (boxes) at various time points after start of imatinib.
relationships between histamine-levels and other disease-parameters. The product limit method of Kaplan and Meier was used to analyze the probability of survival. To calculate the significance of differences between patients with histamine $>100$ ng/ml and those with histamine-levels $\leq 100$ ng/ml or between patients with BCR/ABL $<1\%$ and those with BCR/ABL $\geq 1\%$ at various time points in the follow-up, the pair-wise log-rank test with Bonferroni-correction was applied. Differences were considered significant when $p<0.05$.

results
correlations between histamine and other disease-parameters at diagnosis
The median histamine-level in CML patients at diagnosis amounted to 5,563 ng/ml (range: 181-47,816 ng/ml), and thus was significantly higher compared to age-matched controls (55 ng/ml, 19-108 ng/ml, $p<0.0001$) (Figure 1A). Histamine-levels were higher in patients with CML-AP/ CML-BP (11,242 ng/ml) compared to CML-CP (4,618 ng/ml) ($p<0.05$). As shown in Figure 1B, we found a good correlation between histamine-levels and absolute numbers of basophils ($r=0.87$, $p<0.001$). By contrast, no significant correlations were found between histamine and other disease-parameters (leukocyte-counts, platelets, Ph+ metaphases, BCR/ABL).

hematologic response to imatinib
Of the 80 patients receiving imatinib, 74 (92.5%) showed a complete hematologic response (CHR). When comparing subgroups, the following results were obtained (see Table 2): of the 62 patients with CP, 61 (98.4%) had a CHR. In patients with CML-AP, 12 of 16 patients (75%) entered CHR. In addition 1 of the 2 patients with CML-BP showed CHR during imatinib. In patients receiving imatinib as frontline-therapy, the efficacy of imatinib was higher compared to pretreated patients (Table 2). In fact, all 36 ‘imatinib-frontline-patients’ achieved CHR during imatinib, whereas only 38/44 pretreated patients (86.4%) entered CHR (Table 2). The differences in CHR rates between CML-CP and CML-AP as well as the differences in CHR between previously treated and untreated patients were significant ($p<0.05$).

Figure 3. Histamine-levels during treatment with imatinib. Whole blood histamine-levels were measured before and during treatment with imatinib in 3-month-intervals as indicated. The figure shows histamine-levels in patients with a complete cytogenetic response, CCR (3A), and histamine-levels in patients who did not reach CCR (3B). Results show minimum and maximum histamine-levels (bars), mean (●) and median histamine-levels (–), and the 25th and 75th percentile of histamine (boxes) at various time points after start of imatinib.

Figure 4. Histamine-levels during treatment with imatinib in patients with CML. Blood histamine-levels were measured serially before and during therapy with imatinib by a commercial RIA. The figure shows histamine-levels in a patient with CCR in whom imatinib had to be interrupted for several weeks because of hepatotoxicity (A) and in a patient in CCR who developed a relapse during imatinib-therapy (B). Monitoring of cytogenetic responses was performed by conventional karyotyping (% Ph+ bone marrow metaphases), and monitoring of molecular responses by measuring BCR/ABL using PCR and light cycler technology. The dashed line indicates the histamine cut off level (100 ng/ml).
Of the 80 patients receiving imatinib, 46 (57.5%) entered CCR, namely 40/62 patients with CML-CP (64.5%) and 6/16 patients with CML-AP (37.5%). Of the 36 previously untreated patients, 23 (63.6%) reached CCR, i.e. 21/29 patients (72.4%) with CML-CP and 2/6 patients (33.3%) with CML-AP. In pre-treated patients, 23/44 (52.3%) entered CCR, i.e. 19/33 (57.6%) with CML-CP and 4/10 (40%) with CML-AP. The differences in CCR-rates between CML-CP and CML-AP and between previously treated and previously untreated patients, were significant (p < 0.05). Similar results were obtained when comparing MaCR rates in various groups of patients (Table 2).

**levels of BCR/ABL-transcripts during imatinib-treatment**

Of all 80 patients receiving imatinib, a major molecular response (MMR) was seen in 39 cases (48.8%), i.e. in 34/62 patients with CML-CP (54.8%) and 5/16 patients with CML-AP (31.3%). By contrast, no MMR was obtained in the 2 patients with CML-BP. Of the previously untreated patients (n = 36), 20 (55.6%) were found to enter MMR within 12 months (Table 2). In 19/44 previously treated patients (43.2%), i.e. 16/33 with CML-CP (48.5%) and 3/10 patients with CML-AP (30%), a MMR was found (Table 2). There were clear differences in MMR rates between CML-CP and CML-AP as well as between previously treated and untreated patients, although statistical significance was not reached. However, we found significant differences in molecular responses (at 6 and 12 months) when comparing patients entering CCR (Figure 2A) with those who did not achieve CCR (Figure 2B) (p<0.05).

**histamine-levels during treatment with imatinib**

Before imatinib-therapy, the median blood-histamine-level amounted to 1,184.5 ng/ml (range: 34-33,097 ng/ml).

In previously untreated patients (n = 36; 29 with CML-CP, 6 with CML-AP, and 1 CML-BP), the median histamine-level was 2,088 ng/ml (range: 66-33,097 ng/ml) and thus higher than that in previously treated patients (960 ng/ml; range: 34-24,265 ng/ml).

During therapy with imatinib, histamine-levels decreased and were found to return to normal values (<100 ng/ml; CBR) in most patients. Thus, a CBR was found in 71/80 patients (88.8%), i.e. in 58/62 (93.6%) with CP, in 12/16 (75%) with AP, and in 1/2 with BP. In previously untreated patients, the rate of CBR was 94.4% (34/36). In pretreated patients, imatinib produced a CBR in 37/44 patients (84.1%) (Table 2). There was a difference in histamine-responses at 6 and 12 months when comparing patients entering CCR (Figure 3A) with those who did not achieve CCR (Figure 3B) (p<0.05). Similarly, patients with MMR at 6 months had a lower histamine level (39.5 ± 4.9 ng/ml) compared to patients without MMR (67.2 ± 17.2 ng/ml).

**follow up and correlations between histamine and other disease-parameters during therapy**

Most patients entering CCR showed a continuous MMR and CBR at all time points investigated (Figure 4A). Loss of CCR during treatment was accompanied, followed, or even preceded by a loss of MMR and loss of CBR (Figure 4B). To directly compare MRD variables (Ph+ metaphases, BCR/ABL, histamine), we established correlations and found that blood histamine-levels correlate well with blood-basophils (r = 0.96)
However, we were not able to demonstrate significant correlations between histamine and BCR/ABL (Figure 5B), histamine and Ph+ metaphases (Figure 5C), or between basophils and BCR/ABL (Figure 5D).

prognostic significance of elevated histamine-levels during treatment with imatinib

To examine whether histamine may serve as a prognostic marker, histamine-levels were measured at 3 and 6 months after initiation of therapy. An elevated histamine level (>100 ng/ml) at three or six months was found to be an unfavorable prognostic factor concerning survival in imatinib-treated patients (p<0.05) (Figure 6). A similar prognostic impact was found for BCR/ABL (cutoff 1%), although the prognostic significance of this parameter was evident only after 9 and 12 months, but not at 3 or 6 months (Figure 6C–6F).

resistance against imatinib is an emerging clinical problem in the treatment of CML [17–19]. Therefore, a critical question was whether resistance against imatinib is accompanied or even preceded by an increase in histamine. The results of our study show that histamine-levels indeed increase during or even before the development of a molecular or cytogenetic relapse in these patients.

Monitoring of minimal residual disease (MRD) during treatment with imatinib is an important approach in CML. Usually, monitoring is performed by karyotyping and quantitative PCR [11–16,20–22]. We report on whole blood histamine as an additional MRD-parameter. This test is simple and appears equally sensitive compared to PCR-monitoring. In addition, a persistently elevated histamine level at 3 or 6 months after start of imatinib-therapy is associated with a significantly reduced survival.

![Figure 6](image.png)

Figure 6. Superior prognostic significance of elevated histamine-levels at three months and six months after start of imatinib in CML patients. Histamine levels and BCR/ABL transcript-levels were measured in three-months intervals after start of imatinib therapy. The probability of survival was analyzed using the product limit method of Kaplan and Meier. Patients were separated into those with and without complete biochemical response (<100 ng/ml histamine versus >100 ng/ml) at 3 months (A) and 6 months (B), and those with <1% or ≥1% BCR/ABL at 3 months (C), 6 months (D), 9 months (E), and 12 months (F). To calculate the significance of differences between patients with histamine >100 ng/ml and those with histamine ≤100 ng/ml or between patients with BCR/ABL <1% and those with BCR/ABL ≥1% at various time points, the pair-wise log-rank test with Bonferroni correction was applied. Differences were considered significant when p was <0.05.
A number of different studies have shown that basophilia is an independent prognostic variable in CML [5–8]. In addition, basophilia is an established criterion of disease-acceleration [1,4,5]. However, unfortunately, basophils in CML are often immature, outnumbered by other cells, or extremely suppressed (imatinib) and therefore cannot be easily quantified by morphologic examination. In this regard, blood histamine can be regarded as an important step forward, since histamine is an extremely sensitive parameter and is expressed in immature basophils, and thus is a sufficient objective basophil-parameter.

In addition, our data show that histamine-levels are of prognostic significance. In fact, an elevated histamine level (>100 ng/ml) 3 months or 6 months after start of therapy is associated with a significantly decreased probability of survival. A similar prognostic impact has been described for cytogenetics and BCR/ABL levels measured at 6 or 9 months after starting imatinib [29], which was also confirmed in our study.

The observation that histamine-levels during imatinib correlate well with the numbers of basophils was an unexpected finding. However, the observation that histamine-levels do not correlate with the percentage of Ph+ metaphases or BCR/ABL-levels, was an unexpected result, which may be explained by the fact that basophils and thus histamine decrease at an earlier time-point during treatment compared to BCR/ABL, thereby confirming the prognostic (added) value of histamine.

In summary, our data show that blood histamine is a new interesting and independent MRD variable useful for the monitoring of responses to imatinib. In addition, our data show that elevated histamine at 3 or 6 months after start of therapy (imatinib) is a prognostic parameter.

acknowledgements

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