Quantitative Polymerase Chain Reaction Monitoring of BCR-ABL during Therapy with Imatinib Mesylate (STI571; Gleevec) in Chronic-Phase Chronic Myelogenous Leukemia

Hagop M. Kantarjian,1 Moshe Talpaz, Jorge Cortes, Susan O’Brien, Stefan Faderl, Deborah Thomas, Francis Giles, Mary Beth Rios, Jianqin Shan, and Ralph Arlinghaus

Departments of Leukemia [H. M. K., J. C., S. O., S. F., D. T., F. G., M. B. R., J. J.], Bioimmunotherapy [M. T.], and Molecular Pathology [R. A.], M. D. Anderson Cancer Center, Houston, Texas 77030

ABSTRACT

Purpose: The purpose of our investigation was to evaluate the response and minimal residual disease by quantitative competitive PCR (QC-PCR) studies in patients with chronic myeloid leukemia (CML) treated with imatinib mesylate.

Experimental Design: One hundred eighty patients with Philadelphia chromosome (Ph)-positive chronic-phase CML after IFN-α failure, treated with imatinib mesylate, had 543 simultaneous cytogenetic and QC-PCR analyses at different times during their therapy.

Results: The median QC-PCR values [ratio-percentage of (BCR-ABL/ABL transcripts) × 100] for cytogenetic response categories were: no response (Ph, >90%), 36%; minor response (Ph, 35–90%), 22%; partial response (Ph, 1–34%), 7.3%; complete response (Ph, 0%), 0.89%. There was good correlation between cytogenetic and QC-PCR studies (P < 0.001; r = 0.92) and good concordance between QC-PCR values (>10%, 2–10%, and <2%) and cytogenetic response categories (none, minor, partial, complete) with a concordance rate of 66%, and major discordance of only 10%. Of 170 samples in complete cytogenetic response, 21% still had QC-PCR values of >10%, and 53% had QC-PCR values of <1%. There was excellent concordance between blood and marrow QC-PCR values (r = 0.965; P < 0.01; concordance rate, 88%; major discordance, 0%). No patient in complete cytogenetic response regardless of QC-PCR value has yet relapsed. At a median follow-up time of 26 months, higher QC-PCR values within each cytogenetic category at 3, 6, and 9 months have not been associated with a higher occurrence cytogenetic relapse or disease progression. However, the significance of this may become different with longer follow-up.

Conclusion: QC-PCR studies provide a useful tool to monitor patients with CML on imatinib mesylate therapy.

INTRODUCTION

Suppression of the Ph-positive2-positive cells or the associated molecular events has become the major focus of recent therapies in CML (1–3). This follows the two important observations of (a) the causal association between the BCR-ABL oncogene and its products and the development of CML in preclinical models (4, 5); and (b) the association of achievement of minimal residual disease, i.e., suppression of Ph-positive cells (cytogenetic response) with survival prolongation (6–11). Improved prognosis may also occur with IFN-α (12) and, possibly, with newer therapies such as imatinib mesylate (STI571; Gleevec; Refs. 13, 14) without the suppression of Ph-positive cells, but through the suppression of disease evolution, by analogy to the clinical course of other myeloproliferative disorders such as polycythemia vera or essential thrombocytosis.

Periodic and frequent monitoring of patient response to therapy has become an essential component of disease evaluation, allowing possible modifications of drug dose schedules, addition of other agents, or changing to other therapies, including allogeneic SCT. Thus, monitoring tools that are precise, reliable, reproducible, and easy to perform (e.g., from blood versus marrow samples), have become important to establish in standard laboratory procedures.

Standard cytogenetic studies are presently the accepted standard of monitoring. However, they evaluate usually only 20–25 metaphases, are time consuming, may yield insufficient metaphases in 10–20% of cases, and require bone marrow samples. iFISH techniques improve the monitoring precision (100–200 cells analyzed) and time requirement, but are associated with testing limitations. When the percentage of Ph-positive cells is 90% or more by cytogenetic studies, iFISH may record lower values, suggesting a “cytogenetic response” when it is not present. This may be remedied by using the post:pre-treatment ratio of iFISH values as the percentage of Ph-positive cells. They may also be associated with false-positivity of up to 5–15%, depending on the probes used. Also, the correlation between simultaneous blood and marrow iFISH studies is not precise. Hypermetaphase FISH analysis improves the precision of the measurement (500–1000 metaphases anal-

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1To whom requests for reprints should be addressed, at Department of Leukemia, Box 428, M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030. Phone: (713) 792-7026; Fax: (713) 794-4297; E-mail: hkantarj@mdanderson.org.

2The abbreviations used are: Ph, Philadelphia chromosome; CML, chronic myeloid leukemia; SCT, stem cell transplantation; FISH, fluorescence in situ hybridization; iFISH, interphase FISH; RT-PCR, reverse transcription-PCR; QC-PCR, quantitative competitive RT-PCR.
analyzed and is not associated with false “cytogenetic responses” or false positivity, but requires bone marrow samples. Finally, none of these studies can monitor residual disease at levels of less than 1 in 500-1000 normal cells (15–17).

PCR studies to monitor both response and minimal residual disease have adopted several modifications including a qualitative RT-PCR (18, 19), and quantitative RT-PCR measurements such as the commercial real-time RT-PCR, using for internal controls fluorescent double-stranded DNA dyes or fluorescein probes, or the noncommercial QC-PCR using for internal controls Abl, β-2 microglobulin, or others (15, 20). QC-PCR has been reported to correlate with cytogenetic response and to quantify precisely minimal residual disease (21–23). QC-PCR ratio, the ratio-percentage of BCR-ABL:ABL transcripts × 100, optimized to values >14%, 2–14%, and <2%, have correlated with no cytogenetic response, cytogenetic response, and complete cytogenetic response, respectively. (22) However, the number of patients analyzed in this study was small. QC-PCR has been reported to correlate with cytogenetic response and to quantify precisely minimal residual disease (21–23). QC-PCR ratio, the ratio-percentage of BCR-ABL:ABL transcripts × 100, optimized to values >14%, 2–14%, and <2%, have correlated with no cytogenetic response, cytogenetic response, and complete cytogenetic response, respectively. (22) However, the number of patients analyzed in this study was small. QC-PCR ratios of <0.045 have also correlated with durability of cytogenetic responses on IFN-α therapy (23).

In our studies of imatinib mesylate therapy in chronic-phase CML, we monitored response by both cytogenetic and QC-PCR studies, to evaluate: (a) the correlation between QC-PCR and cytogenetic results; (b) the correlation between simultaneous peripheral and marrow QC-PCR results; and (c) whether QC-PCR values within cytogenetic response categories correlate with cytogenetic relapse or disease progression.

PATIENTS AND METHODS

Study Group and Therapy

Patients with a diagnosis of Ph-positive chronic-phase CML and failure on IFN-α therapy who entered on the Novartis-sponsored multi-institutional Phase II trials and the expanded access studies were evaluated (3, 24). Criteria for entry on studies have been detailed previously (3, 24). Patients signed informed consent according to institutional guidelines. Patients received imatinib mesylate 400 mg p.o. daily. Dose adjustments according to nonhematological and hematological toxicities, and patient monitoring, have been detailed in the therapeutic trials. Samples were obtained for bone marrow analysis including morphology and cytogenetic studies before therapy, every 12 weeks thereafter during the first 12 months of therapy, and for as long as treatment was extended. Molecular studies were performed on blood and marrow studies every 12 weeks. Patients were followed for survival at least every 3 months.

Response Criteria and Statistical Considerations

A complete hematological response (CHR) was defined as normalization of peripheral counts and differential with WBC counts <10 × 10^9/liter, platelets <450 × 10^9/liter, myelocytes and metamyelocytes <5% without blasts or promyelocytes in peripheral blood, and no extramedullary involvement. This was further categorized by the degree of cytogenetic response: complete, Ph-positive metaphases 0%; partial, Ph-positive metaphases 1–34%; minor, Ph-positive metaphases 35–90%. A major cytogenetic response included complete and partial cytogenetic responses, i.e., Ph-positive metaphases 0–34%. At least 20 metaphases were analyzed for each sample before it was considered sufficient for cytogenetic response evaluation.

Cytogenetic and QC-PCR Studies

Cytogenetic analysis was performed by standard techniques (11). For chromosome analysis, bone marrow specimens were examined on direct or short-term (24-h) cultures. At least 20 metaphases were analyzed to consider the cytogenetic analysis and response categorization adequate.

RNA Isolation and cDNA Synthesis. WBCs from patients were isolated from 10–20 ml of peripheral blood or 1–3 ml of bone marrow by treatment with two cycles of ammonium chloride buffer. Total RNA was extracted with Trizol (Life Technologies, Inc.) from about 1 × 10^7 to 1 × 10^8 WBCs or bone marrow mononuclear cells. After measuring the concentration of RNA by a spectrophotometric method (Beckman DU640B; Palo Alto, CA), RNA was transcribed into cDNA using the procedure described previously by Cross et al. (20). The cDNA was stored at −20°C. Competitive nested RT-PCR and real-time RT-PCR were assayed from the same tube of the sample of stored cDNA.

Multiplex RT-PCR. Multiplex RT-PCR was performed to distinguish various BCR-ABL breakpoints described previously (25). In the PCR protocol, cDNA from K562 cell (b3a2), and KBM-7 cells (b2a2) were used as positive controls; KG-1 cells and sterile water (Baxter Co., Deerfield, IL) were used as a negative control. Normal BCR analysis in the multiplex PCR assay was also used as an internal control.

Quantitative Competitive (Nested) RT-PCR. After the BCR-ABL breakpoint was determined, quantitative competitive (and nested if necessary) RT-PCR was performed as described by Cross et al., (20) for BCR-ABL transcripts (b2a2, b3a2) and total ABL. The positive and negative controls were as mentioned above in multiplex PCR; 2.5 μl of cDNA was used in the PCR protocol.

Real-Time Quantitative RT-PCR. The real-time PCR primers and TaqMan probes for amplification and detection of BCR-ABL (b3a2, b2a2) and total ABL were designed by the software of ABI PRISM 7700 Sequence detector (Perkin-Elmer/Applied Biosystems, Foster City, CA). The primers and the probe were as follows for BCR-ABL junctions: (BCR3)b3 sense: CGT CCA CTC AGC CAC AT; (BCR2)b2 sense: TGC AGA TGC TGA TCA ACT CG; and (ABL)a2 antisense: TTC AAC GAG CGG CTT CAC. TaqMan probe for b3a2 and b2a2 was: CAG TAG CAT CTT ACT TTT AGC AGT TCT T, which is derived from ABL exon 2 and lies within the fusion region of the b2a2 and b3a2. Primers and probe for ABL were: ABL sense, GTC TGA GTG AAG CCG CTC GT; ABL antisense, GCC CAC AAA ATC ATA CAG TGC A; and TaqMan probe for ABL, TGG ACC CAG TGA AAA TGA CCC CAA CC. All of the sequences are contained in ABL exon 2.

Real-time quantitative RT-PCR was performed on an ABI PRISM 7700 Sequence detector (Perkin-Elmer/Applied Biosystems, Foster City, CA). Reaction conditions and primer selection for optimal amplification of both BCR-ABL and ABL were determined as described in the manufacturer’s manual; 2.5 μl cDNA templates were added to each tube as with competitive PCR.
Quantitative and Normalization in RT-PCR. For competitive BCR-ABL RT-PCR analyses, a BCR-ABL junction plasmid containing a DNA 100-base insert, developed by Cross et al., was used as a competitor in nested RT-PCR (20). In comparing the competitive quantitative RT-PCR with the real-time RT-PCR, we chose the same plasmid as used in the competitive, quantitative PCR to prepare a standard curve for real-time PCR. The competitor plasmid, serial dilutions were prepared, i.e., $1 \times 10^6$, $1 \times 10^5$, $1 \times 10^4$, $1 \times 10^3$, $1 \times 10^2$, and $1 \times 10^1$ molecules in each µL, respectively. The stock plasmid ($1 \times 10^6$) was stored at 4°C. The diluted plasmids were used for only 1 month. To achieve continuity of the assay results, a cDNA sample with a ratio of 1:100,000 K562:KG-1 cells and a CML-patient sample cDNA, previously analyzed 1 month earlier, were assayed. In addition to determining BCR-ABL transcript levels, each sample was also assayed for total ABL transcripts, either by competitive or by real-time RT-PCR, and the results expressed as a percentage of the ratio of BCR-ABL:ABL, as others have reported.

Samples were assayed initially by real-time RT-PCR to obtain the BCR-ABL:ABL ratio-percentage. If samples were negative by real-time PCR or had very low BCR-ABL transcript values, they were assayed by the more sensitive QC-PCR method (25). The real-time ratio-percentages were very similar to QC-PCR ratio-percentages, but the QC-PCR studies were more sensitive at very low values (26, 27).

RESULTS

One hundred eighty patients with Ph-positive chronic-phase CML and failure on IFN-α therapy, treated with imatinib mesylate on the two studies, had QC-PCR evaluations. Their characteristics and outcome were similar to those of the larger study group detailed elsewhere (3, 23). Their median age was 56.5 years (range, 24–78 years). Overall, 178 patients (99%) achieved a complete hematological response, and 141 (78%) had a cytogenetic response: major in 128 (71%); complete in 56.5 years (range, 24–78 years). Overall, 178 patients (99%) achieved a complete hematological response, and 141 (78%) had a cytogenetic response: major in 128 (71%); complete in 0.89% ($P = 0.001$). The median QC-PCR values in the total study group by duration of imatinib mesylate therapy showed a persistent trend for decreasing QC-PCR values until the 18-month present follow-up time (Table 2).

Correlation of QC-PCR Studies and Cytogenetic Analyses. Quantitative results versus the percentage of Ph-positive metaphases by cytogenetic studies in 363 samples are shown in Fig. 1. In general, there was an excellent correlation between the two analyses ($P < 0.001$, $r = 0.92$). QC-PCR ratios were then compared with cytogenetic studies according to cutoffs of PCR ratios of $>10\%$, 2–10%, and $<2\%$, and cytogenetic responses (none, minor, partial, and complete; Table 3). Again, there was good concordance in these studies [239 (66%) of 363 samples], although major discordances (difference by at least two response categories) were observed in 37 (10%) of 363 samples, and minor discordances (difference by one response category) in 87 (24%) of 363 (Table 3). Of interest, 35 (21%) of 170 samples in complete cytogenetic response still had...
QC-PCR values above 10%, whereas 90 (53%) of 170 had values of less than 1%.

**Correlation of QC-PCR Studies in Marrow Versus Peripheral Blood.** One hundred twenty-six patients had simultaneous peripheral blood and marrow QC-PCR studies. Their correlation is shown in Fig. 2 and in Table 4. Overall, there was an excellent correlation between the QC-PCR marrow and blood studies ($r = 0.965; P < 0.01$) and few discordant values (Table 4; concordance in 110 (88%) of 126; major discordance in 0 (0%) of 126).

**Correlation of QC-PCR Studies with Outcome.** Higher QC-PCR values at 3, 6, or 9 months within particular cytogenetic abnormalities were not associated with subsequent cytogenetic relapse or disease progression (Table 5). In samples showing complete cytogenetic response, QC-PCR values showed a gradual reduction with longer time on therapy: 7 (41%) of 17 patients in complete cytogenetic response tested at 3 months had QC-PCR values <2%, compared with 16 (64%) of 24 tested at 6 months, and 33 (75%) of 44 tested at 9 months ($P < 0.01$). Among the 103 patients who achieved a complete cytogenetic response, only 1 patient had hematological resistance and 2 (3%) patients had cytogenetic relapse; this is compared with 7 patients with hematological resistance and 8 patients with cytogenetic relapse among the 77 patients in other response categories (19%). The three patients with complete cytogenetic response who had progression of cytogenetic relapse did not have QC-PCR studies at the time of complete cytogenetic response evaluation; hence, among the samples in complete cytogenetic response tested by QC-PCR, no cases of hematological resistance or cytogenetic relapse were documented (Table 5).

Among 40 samples showing partial cytogenetic response at 3, 6, or 9 months analyzed by QC-PCR, 3 of 20 with QC-PCR values ≤10% were associated with genic relapse or progression, compared with 2 of 20 with QC-PCR values >10%. Among 59 samples showing minor or no cytogenetic response at 3, 6, or 9 months analyzed by QC-PCR, 1 of 5 with QC-PCR values ≤10% was associated with cytogenetic relapse or progression, compared with 9 of 55 with QC-PCR values >10%.

**DISCUSSION**

Cytogenetic assays continue to be used as the standard for monitoring patients with CML after allogeneic SCT or on IFN-α therapy. However, they have limitations including time consumption, failure to obtain metaphases for analysis in 10–20% of cases, and evaluation of only 20 metaphases. Because the leukemia burden is estimated to be $10^{12}$ leukemia cells at diagnosis, eradication of 2–3 logs of disease to achieve a morphological response reduces the leukemia burden to $10^9$–$10^{10}$ leukemic cells, and a further reduction to 0% Ph-positive cells reduces the burden to $10^7$–$10^8$ leukemic cells. Quantitative RT-PCR analysis has been helpful in patients with minimal residual disease (Ph-positive 0% by routine cytogenetics) to evaluate the potential for long-term event-free survival on IFN-α therapy and after allogeneic SCT (17–22). Quantitative RT-PCR monitoring of residual disease may also determine an increasing level of leukemia burden that may lead to early therapeutic intervention, even in patients who are still in complete cytogenetic remission, if such situations appear to be associated with imminent cytogenetic or hematological relapse.

The significance of quantitative RT-PCR monitoring in patients on imatinib mesylate therapy has not been studied thus far in a large study group. Although the incidence of complete cytogenetic response in patients with chronic-phase CML and IFN-α failure is about 40%, the significance of such a complete cytogenetic response is in relation to those observed with IFN-α therapy or with chemotherapy (e.g., durability) has not been evaluated. Among patients on imatinib mesylate therapy, the validity of a test that predicts for imminent relapse, e.g., by finding a serial increase in QC-PCR value, may suggest multiple possible interventions such as increasing the dose of imatinib mesylate, adding IFN-α cytarabine or homoharringtonine, or choosing the option of allogeneic SCT. In this study, we have investigated several questions in the context of imatinib mesylate therapy: (a) the concordance of peripheral and marrow QC-PCR studies; (b) the concordance of QC-PCR values and cytogenetic response; and (c) the heterogeneity of QC-PCR measurement in patients in complete cytogenetic response, and their correlation with subsequent relapse.

There was an excellent concordance between QC-PCR values of simultaneous peripheral and marrow samples (Fig. 2; Table 4). The concordance rate was 88%, and no major discordances were observed. This suggests that patients may be monitored with peripheral blood samples for quantitative RT-PCR studies. However, marrow periodic studies (e.g., every 6–12 months) may be required to monitor for cytogenetic clonal evolution, and other morphological features of disease progression.
The concordance between established cytogenetic response criteria and QC-PCR values was very good, as shown in Table 3. Concordance between the categories of complete, partial, and no or minor cytogenetic response by cytogenetics versus QC-PCR values of <2%, 2–10%, and >10%, respectively, was 65%; major discordance occurred in only 10% of cases. An important question relates to the prognosis of patients who demonstrate discordant values by cytogenetic versus molecular analyses. For example, in patients in complete cytogenetic response, would high QC-PCR values >10% (persistence of molecular disease) predict for higher rates of relapse or worse survival compared with low QC-PCR values? At this time of follow-up, the QC-PCR values do not appear to predict for a higher rate of relapse within each cytogenetic response (Table 5). For example, among 17 samples in complete cytogenetic response and high QC-PCR values >10%, there were no instances of relapse (Table 5). This suggests either that cytogenetic studies offer better prediction of clinical relapse or that, possibly, the follow-up time is too short to allow for a prediction of relapse by the presence or absence of molecular minimal residual disease by PCR in patients in complete cytogenetic response.

In the total study group, QC-PCR values were associated with differences in outcome. Higher QC-PCR values at 3, 6, or 9 months into therapy were related to a higher occurrence of cytogenetic relapse or disease transformation (Table 5). An interesting question is the significance of high QC-PCR values in patients within a cytogenetic response category as to whether they might predict subsequent cytogenetic relapse and worse outcome. In this study, persistence of high QC-PCR values above 10% with a complete cytogenetic response was 21% (Table 3). With the present follow-up time, only three patients in complete cytogenetic response on this study have shown evidence of cytogenetic relapse or disease progression but did not have QC-PCR studies at the time of complete cytogenetic response. Among patients with lesser degrees of cytogenetic response, higher QC-PCR values were, thus far, not associated with a higher occurrence of cytogenetic relapse or disease progression (Table 5). The prognostic significance of the QC-PCR values within cytogenetic categories may become different within longer follow-up. However, in such patients, therapeutic interventions may presently not be indicated based on the QC-PCR values, within the cytogenetic response categories.

Several preliminary reports have addressed the value of PCR studies in patients with CML treated with imatinib mesylate. Shah et al. (28) analyzed 23 patients in complete cytogenetic response and found 9 to be negative at least once by quantitative RT-PCR, confirming that profound (molecular) remissions are achievable in some patients with CML on imatinib mesylate therapy. Brandford et al. (29) studied 38 patients with CML on imatinib mesylate therapy and showed a good correlation between cytogenetic and peripheral blood real-time RT-PCR results. They also showed that none of 15 patients who had PCR values of >8% at 3 months achieved subsequent complete cytogenetic response, and that the PCR value reduction between months 2 and 3 correlated with subsequent response. Bumm et al. (30) reported real-time RT-PCR studies on 384 samples from 51 patients with CML who were treated with imatinib mesylate. The investigators did not find a good correlation between blood and marrow PCR studies. Initial PCR values predicted for response as follows: 15 of 29 patients with initial BCR-ABL transcripts of <5000 molecules/a Mol/GAPDH and only 2 of 20 with higher values achieved major or complete cytogenetic response. In analyzing 31 patients with CML in complete cytogenetic response, Lin et al. (31) reported that the median real-time RT-PCR value was 0.052% (range, 0–0.7); that none of the patients, thus far, had a re-increase of PCR values; and that, concordant with their prior experience, PCR values were <2% in all of the complete cytogenetic responders. Press et al. (32) studied 51 patients with CML on imatinib mesylate therapy and found good correlations between quantitative RT-PCR values and cytogenetic or FISH studies, as well as excellent correlations between blood and marrow PCR values. Bories et al. (33) also found a good correlation between cytogenetic and real-time RT-PCR studies and a rapid reduction of BCR-ABL transcript levels with imatinib mesylate therapy compared with IFN therapy. Clark et al. (34) studied 38 patients with CML on imatinib mesylate therapy and found a good correlation between cytogenetic and real-time RT-PCR studies. Unlike our study, they did not observe any patients with discordant PCR and cytogenetic results. Finally, Merx et al. (35) analyzed 364 peripheral blood samples in 106 patients with CML treated with imatinib mesylate on the German studies. They reported an excellent correlation between cytogenetic and real-time RT-PCR studies (r = 0.68; P < 0.001) and found that the BCR-ABL:ABL ratio at 2 months predicted for the 6-month major cytogenetic response rate (P = 0.006), and that all complete cytogenetic responders were still PCR positive at the time of follow-up.

In summary, our study suggests a significant benefit from monitoring patients with CML on imatinib mesylate therapy by using QC-PCR analyses. Good correlations were demonstrated

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<th>Table 4</th>
<th>Correlation of QC-PCR values in blood and marrow simultaneous studies</th>
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<tr>
<td>QC-PCR in blood</td>
<td>No. (%) QC-PCR in marrow</td>
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<tr>
<td>&gt;10%</td>
<td>2–10%</td>
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<td>&gt;10%</td>
<td>48 (58)</td>
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<td>&lt;2%</td>
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<th>Table 5</th>
<th>Correlation between QC-PCR values and outcome in patients within cytogenetic response categories at 3, 6, and 9 months</th>
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<td>QC-PCR at 3, 6, or 9 months</td>
<td>No. of patients at 3 mo/6 mo/9 mo</td>
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<tr>
<td>Complete cytogenetic response</td>
<td>&lt;2%</td>
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<td>Partial cytogenetic response</td>
<td>&lt;2%</td>
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<td>Minor or no cytogenetic relapse</td>
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between cytogenetic and QC-PCR values, despite some discordant results, the significance of which remains unknown. There was also a good correlation between peripheral and marrow QC-PCR studies, as well as heterogeneity of QC-PCR values within classical cytogenetic response categories, an observation that may have future potential prognostic relevance.

REFERENCES


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