Practical Monitoring of Chronic Myelogenous Leukemia: When to Change Treatment

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Abstract

In patients with chronic myelogenous leukemia (CML) treated at diagnosis with the standard therapy consisting of imatinib, 400 mg once daily, the failure to achieve a complete cytogenetic response (CCyR) within 12 months from the start of therapy has been shown to be associated with an increased risk of progression and an overall inferior survival. Experts of the European LeukemiaNet and NCCN have indicated what degrees of hematologic, cytogenetic, and molecular responses should be expected at definite time points for patients with CML to have the highest probability of experiencing the final optimal response, defined as the achievement of at least a complete hematologic response with a minor cytogenetic response after 3 months; at least a partial cytogenetic response after 6 months; at least a CCyR after 12 months; and a major molecular response after 18 months of therapy. The last opportunity for a CCyR has been established at 18 months. Because the residual probability of attaining a CCyR is reduced for patients who do not experience a complete hematologic response by 3 months, any cytogenetic response by 6 months, or a major cytogenetic response by 12 months, these conditions are considered treatment failures. At this point, a change in therapy is highly recommended, such as second-line treatment with the second-generation tyrosine kinase inhibitors nilotinib or dasatinib and, in specific situations, a stem cell transplant. The loss of any grade of previously achieved cytogenetic response at any time point is also considered an imatinib failure demanding a change of therapy. Finally, intermediate gradations of response exist between optimal response and failure in which, although not totally compromised, the possibilities of achieving an optimal response later are decreased. The best therapeutic strategies to be followed in these intermediate situations, called suboptimal responses, have not been clearly established and are still under clinical investigation, but for the moment, a change of therapy is not required. (JNCCN 2012;10:121–129)

Chronic myelogenous leukemia (CML) is a clonal stem cell disease characterized by the presence of the BCR-ABL oncogene, whose endowed and constitutively activated tyrosine kinase activity leads to increased proliferation and genomic instability of the affected clone. In the absence of adequate therapy, the natural history of the disease is inevitable progression from an initial chronic phase, lasting a variable length of time (from a few months to 5–6 years, with a median of 3–4 years) and characterized by the presence of immature myeloid progenitors in peripheral blood, to a highly aggressive acute phase (blast crisis). The acute phase is characterized by the presence of more than 20% to 30% undifferentiated myeloid or lymphoid blasts in the bone marrow or peripheral blood, and the clinical outcome of these patients is usually fatal, even today. Data from many clinical trials show that specific degrees of leukemic mass reduction in response to therapy strictly correlate with the risk of progression and are the most important prognostic factor for the long-term outcome of patients with CML. This concept was first shown for patients treated with interferon-α, the first agent capable of inducing a substantial number of good cytogenetic responses in patients with CML, and it has been substantially validated in patients treated with imatinib and other tyrosine kinase inhibitors (TKIs). However, in...
the presence of a similar degree of leukemic burden reduction, whether the risk of progression is different with different drugs is currently unknown.

In recent years, the impressive response rates and good tolerability have led to imatinib becoming the standard frontline therapy for patients with CML in early chronic phase. At 8-years’ follow-up, the International Randomized Study of Interferon and ST1571 (IRIS) study showed a complete cytogenetic response (CCyR) in 83% of patients and a projected overall survival of 85%. The latter result is mainly from a substantial decrease in the number of deaths caused by progression of CML. This phenomenon can certainly be ascribed to the great reduction of the leukemic mass observed in most patients treated with imatinib, but probably also partly to a slowing effect on the genomic instability of the Ph-positive clone exerted by imatinib through inhibiting the BCR-ABL tyrosine kinase activity. Currently, the residual propensity of the Ph-positive clone to progress in an individual patient with CML cannot be monitored, and therefore one is limited to monitoring response in terms of leukemic burden reduction.

Furthermore, adequate follow-up and a sufficient number of observations to establish a reasonable association between the degree of response and the final outcome are currently only available for patients treated with imatinib, 400 mg once daily, as first-line therapy. For patients treated with second-generation TKIs as first-line therapy, the number of observations is still limited and the follow-up is too short to allow definitive conclusions.

Assessment of Leukemic Load Reduction With Standard Imatinib Therapy

Optimizing CML treatment with TKIs requires an appropriate and timely follow-up using adequately reliable methods to determine hematologic, cytogenetic, and molecular responses. The return to normal hematologic parameters (hematologic remission) without any grade of cytogenetic remission does not produce a substantial advantage in terms of prognosis, because it does not prevent the natural tendency of the disease toward progression. In the interferon era, cytogenetic response was established as the most important prognostic parameter to evaluate in patients with CML, and this remained true even after the advent of imatinib. However, the high percentages of CCyR obtainable with imatinib led to molecular monitoring of BCR-ABL transcript levels with real-time quantitative polymerase chain reaction (RQ-PCR) as one of the preferred methods to assess the residual amount of disease in patients, particularly those experiencing CCyR. This method may allow patients with CCyR to be further stratified into subgroups with different outcome features, although not in terms of overall survival.

Finally, it was established that mutations in the BCR-ABL kinase domain represent the most frequent event associated with resistance to imatinib, and in general to TKIs. In some instances, detection and characterization of these mutations have been shown to allow timely and appropriate treatment intervention, and therefore mutation detection is becoming part of the armamentarium for correct follow-up of patients with CML.

Hematologic remission is obtained when the platelet count is less than 450/L and the WBC count is less than 10/L, the differential count does not present immature granulocytes, basophils are less than 5%, and the spleen is not palpable. The simple achievement of hematologic remission without cytogenetic remission does not substantially reduce the initial leukemic burden (<1-log), which begins to decrease in a proportional and substantial way only with the achievement of a subsequent cytogenetic response. The degree of cytogenetic response is established based on the percentage of the Ph-positive metaphases out of a minimum of 20 metaphases analyzed. Cytogenetic response is defined as complete (CCyR) when 0%, partial (PCyR) when 1% to 35%, minor when 36% to 66%, and minimal when 67% to 95% of residual Ph-positive metaphases are still present. Major cytogenetic response (MCyR) is the sum of CCyRs and PCyRs. Achievement of CCyR corresponds roughly to a reduction of 2-logs in the total amount of leukemic clones compared with what was medially present at diagnosis. After CCyR, the amount of persistent disease can be estimated by the level of the BCR-ABL transcripts measured with RQ-PCR, which has been determined to be proportional to the number of residual leukemic cells. The sensitivity that can be reached with the present RQ-PCR procedures in a sample of good quality is approximately $1 \times 10^{-5}$, which corresponds to an amount between 2- and 3-logs below
the threshold of achievement of CCyR. Two levels of BCR-ABL transcripts in particular have been associated with some prognostic features: major molecular response (MMR) and complete molecular response (CMR). The concept of MMR was first introduced by the IRIS investigators as a level of BCR-ABL equal to or more than a 3-log reduction from a median baseline amount of BCR-ABL present at diagnosis, calculated by pooling together 30 peripheral blood samples from patients with untreated CML. As in the later established international scale (IS), the original standardized baseline is taken to represent 100% BCR-ABL; MMR (3-log reduction) corresponds to 0.10% BCR-ABL, and the threshold of CCyR corresponds roughly to 1% BCR-ABL.

The definition of CMR (previously defined as the absence of detectable BCR-ABL transcripts by nested real-time polymerase chain reaction [RT-PCR] in a sample of sufficient quality to allow a sensitivity of at least 10^4) is currently confusing and under revision because it is clear that “complete” is not really complete but simply dependent on the sensitivity that can be reached in a given sample. Therefore, the term CMR will probably be substituted by the indication of the real amount of residual disease present in the samples, and the results expressed as MR^3, MR^5, and MR^3, which correspond, respectively, to a decrease of 4+, 4.5+, or 5-logs with respect to the median standard baseline at diagnosis, and to a percentage of 0.01%, 0.0032%, or 0.001% of BCR-ABL according to the IS (Cross NP, Hochhaus A, Muller M, et al., manuscript in preparation, 2012). Because differences among methods can lead to variation in measurement, several attempts to standardize the RQ-PCR and reliably express the results according to the IS have been undertaken recently.

To effectively monitor therapeutic responses over time, hematologic remission should be evaluated every 2 weeks until a complete hematologic remission has been achieved and confirmed, and a conventional cytogenetic examination of marrow cells should be performed at diagnosis; 3, 6, and 12 months; and then at least every 6 months until CCyR has been achieved. Most clinicians, outside clinical trials, could be hesitant to perform a cytogenetic analysis at 3 months to simply document the presence or absence of an initial cytogenetic response (see later discussion) without clear indications of the therapeutic decisions to be driven by this finding. However, increasing data are showing that a fast initial response may be highly predictive of final outcome.

Although the effect of an imatinib dose increase or a switch to second-generation TKIs at 3 months on the achievement of different final end points remains to be established, a more-intense schedule for monitoring response with cytogenetic or molecular analysis within the first semester of therapy is advisable, even in common clinical practice, and will probably be reinforced in future recommendations. Afterward, once MMR has been obtained, conventional cytogenetic examination of marrow cells may be performed only when a consistent rise in BCR-ABL transcript level is observed or in special circumstances, such as in the presence of clonal chromosomal abnormalities in the Ph-negative cell population (present in approximately 5% of patients in CCyR) or, as recommended by the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for CML, in the presence of unexplained or prolonged cytopenias (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org). This, in fact, could represent an early sign of progression to blast crisis or the presence of a myelodysplastic or leukemic process originating in the Ph-negative population, which, although rare, has been reported.

Monitoring cytogenetic response through fluorescence in situ hybridization (FISH) analysis of blood cells is still debated. Few studies have compared conventional cytogenetics and FISH analysis on marrow and/or blood cells, and cytogenetic analysis is still needed to detect additional chromosome abnormalities (ACA) in the Ph-positive clone or other chromosome abnormalities (OCA) in the Ph-negative population. Therefore, FISH currently must be considered complementary and not an alternative to conventional cytogenetic analysis. However, in patients who are BCR-ABL–positive but lack the presence of a classical Ph-chromosome, or even when cytogenetic analysis fails, FISH may represent a useful method to complement and confirm the data obtained with RQ-PCR.

Qualitative RT-PCR should always be performed at diagnosis to identify the type of fusion present in the BCR-ABL transcripts and to see if conventional RQ-PCR analysis will be applicable to monitor the response of an individual patient. RQ-PCR analysis...
is not necessary at diagnosis, but should be performed every 3 months to monitor response until the patient achieves at least a stable MMR.\textsuperscript{10} Ideally, BCR-ABL transcript levels should be measured at 3-month intervals even after the achievement of MMR, but measurements at intervals no longer than 6 months are acceptable.\textsuperscript{10} This long-lasting and actually unlimited follow-up of patients with RQ-PCR is essential to verify whether the transcripts continue to decline and eventually become undetectable, reach a rather stable plateau, or, more importantly, tend to increase, which has been associated with the onset of resistance or lack of adherence to therapy.\textsuperscript{26–28} The definition of a significant rise in BCR-ABL levels is still debated, and real consensus does not exist regarding when and which actions must be elicited in these circumstances. However, in this setting, criteria found to be clinically significant to trigger mutation analysis and that should prompt at least a more stringent follow-up of the patient include loss or no achievement of MMR and more than a 1-log increase in RQ-PCR values (see later discussion).\textsuperscript{28}

**Response-Driven Therapeutic Decisions: When is it Convenient to Change Therapy?**

Response in patients with CML is a dynamic concept and must be considered in relation to the time elapsed from the start of therapy. Failure to achieve a certain degree of reduction of leukemic burden within a definite time in a patient with good compliance to therapy indicates the presence of a more resistant (and potentially also more advanced) disease, and that the patient is at greater risk of progression.\textsuperscript{29} Although progression will not necessarily occur, patients have a reduced chance of achieving a disease status associated with minimal risk of subsequent relapse and/or progression while continuing the same therapy.\textsuperscript{10,29} This is generally referred to as primary resistance, whereas secondary resistance is the confirmed loss of any previously achieved degree of cytogenetic or molecular response.

A panel of international experts on behalf of the European LeukemiaNet (ELN)\textsuperscript{10,30} and members of the NCCN\textsuperscript{11} have indicated what degree of hematologic, cytogenetic, and molecular responses should be expected at definite time points for patients who are treated at diagnosis with the standard therapy of imatinib, 400 mg once daily, to have the lowest potential risk of progression or of not achieving the desired final response. Table 1 lists the parameters that ELN and NCCN use to define failure and suboptimal response at each time point, and the consensus and differences between the groups.

Optimal response to imatinib therapy is considered at least a CCyR after 12 months of treatment, because this target has been shown to be sufficient for indicating the highest probability of long-term survival.\textsuperscript{10,11,15} Therefore, the dynamics of the cytogenetic response within the first year of therapy still represent the strongest prognostic parameter for evaluating response. Because the residual probability of obtaining a CCyR at 12 months is really reduced for patients who do not achieve a complete hematologic response by 3 months or any cytogenetic response by 6 months, these conditions are considered treatment failures according to ELN and NCCN criteria, and a change in therapy is highly recommended.\textsuperscript{10,11,29} Although not totally compromised, the chances of achieving a CCyR at 12 months are also decreased if the patient has not attained at least a minor cytogenetic response at 3 months and at least a PCyR at 6 months. This condition has been termed suboptimal response\textsuperscript{10} to define an intermediate situation in which the reduction of the Ph-positive clone is slower than expected but substantial possibilities remain for it to be achieved in the future, and therefore a change in therapy is not necessarily required.

The last opportunity to achieve a CCyR has been established at 18 months, and the lack of a CCyR after this time, the lack of an MCyR by 12 months, or the loss of any grade of previously achieved cytogenetic response at any time points are also considered imatinib failures, but the presence of a PCyR at 12 months is still considered a suboptimal response.\textsuperscript{10,11}

Failure to achieve a cytogenetic response on imatinib strongly demands a change in treatment,\textsuperscript{10,11,29} including a switch to one of the available second-generation TKIs, dasatinib or nilotinib, whose efficacy as second-line therapy in patients with imatinib-resistant or imatinib-intolerant CML has been clearly shown in several phase II studies.\textsuperscript{31,32} The best therapeutic strategy to follow for patients with cytogenetic suboptimal response, however, has not been clearly established. A wait-and-watch strategy, an imatinib dose increase to 800 mg once daily, or an immediate switch to a
## Table 1 European LeukemiaNet and NCCN Parameters to Define Failure and Suboptimal Response

<table>
<thead>
<tr>
<th>Monitoring</th>
<th>Response Evaluation</th>
<th>Suggested Actions</th>
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<tbody>
<tr>
<td><strong>Diagnosis</strong></td>
<td>Requested: Hematologic parameters Spleen size Bone marrow cytogenetics RT-PCR</td>
<td>Requested: Hematologic parameters every 2 wk until CHR achievement, then every mo until the third mo, and then every 3 mo</td>
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<tr>
<td></td>
<td>Optional: RQ-PCR FISH</td>
<td>Optional: RQ-PCR every mo for the first 3 mo</td>
</tr>
<tr>
<td><strong>Month 3</strong></td>
<td>Requested: Hematologic parameters Spleen size Bone marrow cytogenetics* RQ-PCR</td>
<td>Optimal Response: At least CHR minor CyR* Suboptimal Response: CHR, but no minor CyR* Failure: No CHR</td>
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<tr>
<td></td>
<td>Optional: FISH</td>
<td></td>
</tr>
<tr>
<td><strong>Month 6</strong></td>
<td>Requested: Bone marrow cytogenetics RQ-PCR</td>
<td>Optimal Response: At least PCyR</td>
</tr>
<tr>
<td></td>
<td>Optional: FISH</td>
<td>Suboptimal Response: Less than PCyR Failure: No CyR</td>
</tr>
<tr>
<td><strong>Month 12</strong></td>
<td>Requested: Bone marrow cytogenetics RQ-PCR</td>
<td>Optimal Response: At least CCyR</td>
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<tr>
<td></td>
<td>Optional: FISH</td>
<td>Suboptimal Response: PCyR Failure: Less than PCyR</td>
</tr>
<tr>
<td><strong>Month 18</strong></td>
<td>Requested: Bone marrow cytogenetics if not already CCyR or in case of OCA RQ-PCR</td>
<td>Optimal Response: CCyR with MMR Suboptimal Response: CCyR but no MMR Failure: Less than CCyR</td>
</tr>
<tr>
<td></td>
<td>Optional: FISH</td>
<td></td>
</tr>
<tr>
<td><strong>Beyond Month 18</strong></td>
<td>Requested: RQ-PCR every 3 mo if not MMR; at least every 6 mo if MMR Bone marrow cytogenetics every 6–12 mo if not already CCyR or in case of OCA</td>
<td>Optimal Response: Persistent MMR or CMR Suboptimal Response: Loss of MMR Failure: Loss of CCyR</td>
</tr>
</tbody>
</table>

Abbreviations: CHR, complete hematologic response; CMR, complete molecular response; CCyR, complete cytogenetic response; CyR, cytogenetic response; FISH, fluorescence in situ hybridization; MMR, major molecular response; OCA, other chromosomal abnormalities; PCyR, partial cytogenetic response; RQ-PCR, real-time quantitative polymerase chain reaction; RT-PCR, real-time polymerase chain reaction; TKI, tyrosine kinase inhibitor. *Only recommended by European LeukemiaNet.
second-generation TKI are still possible options, because currently no clear clinical evidence shows that one strategy provides substantial advantages over another in terms of overall or progression-free survival. However, reports that cytogenetic suboptimal responses have final outcomes not so dissimilar from those of manifest failures, the good results obtained with second-generation TKIs, and these agents’ good tolerability as both second- and first-line therapy in CML are progressively moving many clinicians in the countries where these drugs are available to favor switching to second-generation TKIs.

Current data do not support the notion that achieving an MMR may improve overall survival relative to achieving a CCyR without an MMR. However, many studies since IRIS have subsequently shown that the achievement of an MMR is associated with several advantages that could influence the long-term outcome of patients with CML. The statistically significant better event-free survival observed at 72 months in the IRIS study for patients with a CCyR and MMR compared with those with a CCyR but no MMR by 18 months was apparently not confirmed in other studies. However, achieving an MMR in addition to a CCyR was established to significantly decrease the risk of subsequently losing CCyR and of progression, and has been reported to be associated to a more stable response. A fast achievement of an MMR also has been associated with a higher probability of achieving a CMR, and a prolonged CMR of at least 2 years has been shown to offer the possibility of discontinuing imatinib without molecular relapse. Thus, achievements of MMR and CMR are appealing targets to pursue, because they are predictive of more durable and stable responses. A CMR, in particular, can also offer the possibility of stopping therapy.

Based on the previous elements, current recommendations by the ELN indicate that an MMR is the optimal response to be achieved by 18 months. However, they do not consider no achievement of MMR or loss of MMR without loss of CCyR to be a treatment failure, but rather a suboptimal response only, because currently no clinical evidence shows that any change in therapy, such as switching to a second-generation TKI, could improve the long-term outcome of these patients. The only exception to this indication is when no achievement or loss of MMR is associated with the presence of mutations poorly sensitive to imatinib, such as T315I, E255K/V, or Y253H. These situations are considered failures and should therefore prompt appropriate changes in therapy.

The ELN recommends mutational analysis not only in all instances of failure but also in cases of suboptimal response. The reason for this is that it is progressively becoming clear that in these situations the presence of BCR-ABL mutated clones suggest the presence of true resistance, which could more likely indicate a change in treatment rather than an imatinib dose increase. Furthermore, mutation analysis could also help determine the more appropriate therapeutic choice, such as which second-generation TKI to use and whether stem cell transplantation is appropriate.

Mutations seem to be more frequently associated with secondary resistance than primary. Importantly, until low amounts of residual disease are achieved, a reduced but actual risk of loss of response or even progression may remain, even in patients apparently experiencing a timely and appropriate response to therapy. This underlines the fact that a very fast decrease of the residual disease to levels associated with more stable responses and with less risk of progression is always desirable and should be resolutely pursued, at least in circumstances associated with a higher risk of progression. Unfortunately, apart from the parameters to recognize and consider primary resistance, no good markers currently exist to identify patients prone to develop secondary resistance or progression, although both types of resistance seem to be more frequent in patients who present at diagnosis with the clinical and hematologic parameters used to stratify according to prognostic risk scores (Sokal, Euro, and the new European Treatment and Outcome Study for CML [EUTOS] scores). Nevertheless, currently no treatment recommendations specific for intermediate- or high-risk patients have been suggested, but a more detailed analysis of the data emerging from the clinical studies comparing standard-dose imatinib versus nilotinib or dasatinib as first-line therapy could also modify this vision in the future.

Conclusions and Final Considerations

The introduction of imatinib was of paramount importance in the treatment of CML, totally changing the survival perspectives of most patients, although
they remained drug-dependent for an indefinite time. In the past decade, clinicians have progressively learned to optimize therapy with imatinib, and have established rather precise and useful parameters to achieve the best possible outcome in terms of overall, progression-free, and event-free survival by changing treatment for patients who were intolerant of or resistant to imatinib therapy to a more potent second-generation TKI (dasatinib or nilotinib).

More recently, however, 2 observations, although rather preliminary, seem to challenge the current vision regarding the target to achieve in CML therapy. The first is the possibility for some patients obtaining a CMR to discontinue the therapy without experiencing disease recurrence, at least for a short but relevant follow-up. The second is that when nilotinib and dasatinib have been compared with standard-dose imatinib as first-line therapy of CML, they showed increased capacity to induce a faster and higher rate of MMRs and to prevent some of the progression events that occur during the first months of imatinib therapy, and also the ability to substantially improve the percentage of patients obtaining a CMR, suggesting a possible definitive cure in a substantial number of patients.

Currently, taking patients off therapy outside specific investigational trials is not advisable, because some patients experience relapse, and whether these relapses are risk-free is uncertain. It is likely, however, that better parameters will be available in the future to identify patients with a very high probability of not experiencing relapse after discontinuation. These parameters will certainly include factors related to the leukemic clone (e.g., residual amount, propensity to expand), but also those related to the host, such as the capacity to mount an immune response through expanding T-cell clones targeting the leukemic cells, as recently shown by the detection of PRI1-specific T cells in patients with CML who show unmaintained cytogenetic remission after interferon withdrawal. Furthermore, a better understanding of the mechanisms leading to CML leukemic stem cell survival despite the TKI therapy, such as the recently reported “rescue” exerted by cytokines in the bone marrow hematopoietic niches, will create the possibility of achieving a CMR and, consequently, reaching a definitive cure. Nevertheless, within a certain limit and comparable probabilities of overall survival, the definition of the optimal response to be reached by patients with CML remains relative and must take into consideration the balance between the potential benefits and the costs (not only economic) of the therapeutic approach for individual patients. For an elderly patient, obtaining an overall survival probability that overlaps that of a control population without CML could be an acceptable target, and convenient if associated with a therapy that is better tolerated. Alternatively, the expectations may be different for a younger patient who wants to pursue a definitive cure without needing to continue the therapy indefinitely, even if it means changing to a more demanding therapeutic approach.

Evidence is not yet available showing that using the more potent second-generation TKIs, which are able to lower the number of patients whose disease is resistant or progresses to accelerated or blast phase during the first months of therapy, instead as first-line therapy will translate into a significantly better overall survival, but the follow-up is still short. These trials do not even have a sufficiently long follow-up to evaluate parameters predictive of response or outcome. Although the canon “faster and deeper responses are better” may be supported by several sets of data, this may not always be the case. This is seen in the trials testing 800 mg versus 400 mg of imatinib, in which the faster achievement of an MMR observed at 6 months in the 800-mg arm was later reached by the 400-mg arm, without any substantial advantage in terms of overall, event-free, and progression-free survivals. Therefore, it will be important to evaluate whether time-related parameters of response to the second-generation TKIs when used as first-line therapy will translate into substantial clinical benefits. To obtain correct information, it will also be very important to define precisely the event-free and progression-free survival end points, which have been shown to change substantially in different trials and to introduce important bias in the evaluation of results.

Currently, however, apart from investigational trials with one of the third-generation TKIs under development, or allogeneic stem cell transplant in patients with a donor who can be moved conveniently to a stem cell transplant procedure, alternative therapeutic options are not registered for patients for whom second-generation TKIs are failing as first-line therapy. Therefore, patients without an optimal response but no disease progression or loss
of hematologic remission could remain on the same therapy unless a specific reason exists to discontinue the treatment with that specific TKI or a TKI therapy in general.

References


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