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ONCOLOGY GRAND ROUNDS

Patient With Chronic Myeloid Leukemia in Complete Cytogenetic Response: What Does It Mean, and What Does One Do Next?

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See accompanying articles on pages 415 and 424

The Oncology Grand Rounds series is designed to place original reports published in the Journal *into clinical context. A case presentation is followed by a description of diagnostic and management challenges, a review of the relevant literature, and a summary of the authors' suggested management approaches. The goal of this series is to help readers better understand how to apply the results of key studies, including those published in* Journal of Clinical Oncology, *to patients seen in their own clinical practice.*

A 57-year-old man was diagnosed with chronic myeloid leukemia (CML) in chronic phase (low Sokal risk) in April 2003 after a routine blood count showed a WBC count of 17,723/μL. He was administered imatinib 400 mg daily and rapidly achieved normal blood counts. At 3, 6, and 12 months, the *BCR-ABL1*/*ABL1* transcript ratios in peripheral blood were 1.8%, 1.02%, and 0.5%, respectively (Fig 1). Bone marrow examination performed at 6 months showed 100% Philadelphia chromosome–negative metaphases. The only adverse effect attributable to imatinib was persistent mild asthenia. Thereafter, the transcript level declined further, but between October 2005 and July 2008, it plateaued at approximately 0.07%; the patient was then advised to switch to nilotinib 400 mg twice per day to obtain a deeper molecular response (MR). One year later, the patient developed symptoms of intermittent claudication requiring angioplasty in both popliteal arteries. Nilotinib was discontinued, and the patient was referred to our center for further management. The transcript level was then 0.025%. We recommended that he restart imatinib at a reduced dose (300 mg per day) because of his prior asthenia while receiving treatment. The patient achieved complete MR (CMR) 30 months after the reintroduction of imatinib. Six months later, he asked about the possibility of discontinuing imatinib because of persistent asthenia (although this adverse effect was less severe than when receiving the full dose). Imatinib was discontinued, and he remained in CMR for 6 months before *BCR-ABL1* transcripts were detected on two consecutive tests, at 0.004% and 0.003%, respectively. The management question became: Should the patient resume tyrosine kinase inhibitor therapy?

CHALLENGES IN DIAGNOSIS AND MANAGEMENT

A majority of patients with newly diagnosed chronic myeloid leukemia (CML) treated with tyrosine kinase inhibitors (TKIs) achieve complete cytogenetic responses (CCyRs) within 12 months of starting therapy. They are classified as good responders, and their life expectancy is believed to be akin to that of healthy individuals.[1,2] In these patients, *BCR-ABL1* transcript levels are monitored to assess the quantity of residual leukemia, and results are often expressed as the $\log_{10}$ reduction from a standardized value for untreated patients or more recently by using the international scale (IS), where 100% is the arbitrary value for a hypothetic untreated patient at diagnosis.[3,4] Table 1 lists the definitions of molecular responses (MRs).

There is enormous variability in the degree of MR that patients may achieve after CCyR.[7] For example, some patients may achieve CMRs, whereas other patients in CCyR may not even achieve MR3. This variability in response represents a challenge for physicians for a number of reasons. First, it is not clear which of these response levels should be the target of therapy, because overall (OS) and progression-free survival (PFS) seem equally good irrespective of whether the patient achieves MR3, MR4, MR4.5, or CMR. Although it seems intuitive that a patient with deeper MR would fare better in the long term than one with lesser response, this remains entirely unproven and, to date, unsupported by clinical data. Second, although the biologic reasons for this variability are unclear, patient adherence to TKI therapy plays a major role in determining the level of response.[8] Third, even if we choose to aim for a given level of MR as the target of therapy, it is not clear what should be done if the patient fails to achieve this target, because there are no data from randomized studies showing that patients

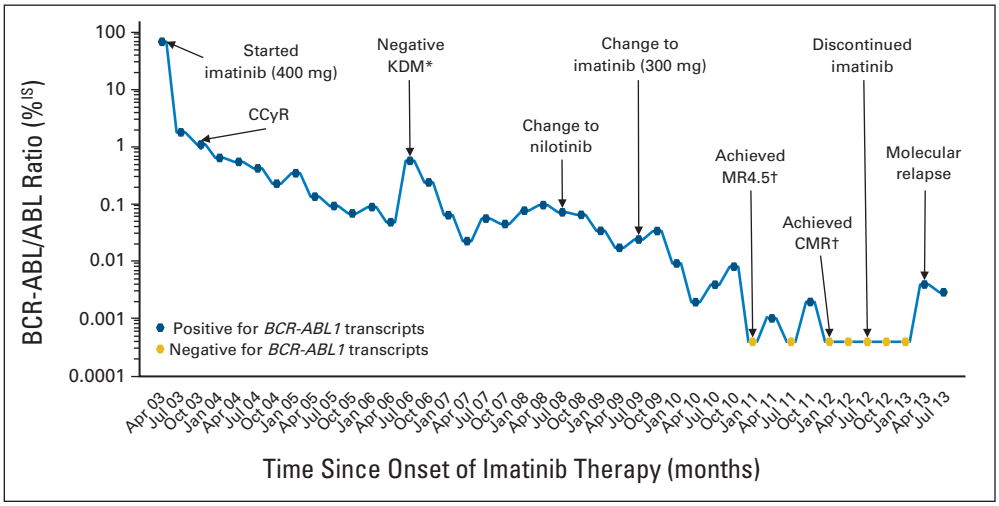

Fig 1. Evolution of *BCR-ABL1* transcript level in peripheral blood. (*) Kinase domain mutation (KDM) analysis was performed, which was negative. (†) Achievement of molecular response 4.5 (MR4.5) or complete molecular response (CMR) requires two consecutive results below MR4.5 or CMR threshold. CCyR, complete cytogenetic response.

who have not achieved a given molecular milestone with a particular TKI may achieve that milestone if the therapy is changed. Fourth, we are unable to reliably identify which patients may safely discontinue TKI therapy, or at what threshold. Only a minority of patients achieve sustained CMRs (likely between 10% and 30% of patients), and only 40% of them can discontinue TKI therapy permanently without relapse,[9-11] suggesting that discontinuation is a not realistic treatment goal for all patients with newly diagnosed CML.

SUMMARY OF THE RELEVANT LITERATURE

In the majority of patients who achieve CCyRs, *BCR-ABL1* transcripts continue to decline.[7] In the early days of TKI use, researchers tried to establish whether this further reduction in the leukemia burden conferred any survival advantage. Hughes et al[12] analyzed data from patients who received imatinib as initial therapy in the IRIS (International Randomized Study of Interferon and STI571) trial and

Table 1. Working Relationship Between Leukemia Burden, *BCR-ABL1* Transcript Levels, and Molecular and Cytogenetic Responses

Leukemia Burden (No. of cells)	Ph-Positive Metaphases (%)	Cytogenetic Response	*BCR-ABL1*/*ABL1* (%IS)	MR	Comments
$> 10^{12}$	Variable, normally > 90	No response	Variable, normally > 40	No response	Status at diagnosis; most patients are 100% Ph-positive at diagnosis, and transcript level is close to 100%
Approximately 10^{11}	≤ 35	MCyR	10	MR1	
Approximately 10^{10}	0	CCyR	1	MR2	No detectable Ph-positive marrow metaphases
Approximately 10^{9}	0	CCyR	0.1	MR3	Also known as MMR
Approximately 10^{8}	0	CCyR	0.01	MR4	Most laboratories consider that minimal number of copies for control gene must be ≥ 10,000 for valid transcript measurement, so minimal level of sensitivity of any transcript measurement is normally 10^{-4}
Approximately 6×10^{7}	0	CCyR	0.0032	MR4.5	To define MR4.5, ratio has to be ≤ 0.0032%, or transcripts must be undetectable, with copy numbers for control gene ≥ 32,000
Approximately 10^{7}	0	CCyR	0.001	MR5	To define MR5, copy number for control gene must be ≥ 100,000
$< 6 \times 10^{7}$	0	CCyR	Not detectable	CMR	CMR is generally defined as absence of detectable *BCR-ABL1* transcripts, with control gene copy numbers ≥ 40,000, although some laboratories have stricter criteria (ie, control gene must be ≥ 100.000 copies); number of copies of control gene determines level of sensitivity of assay

NOTE. Correspondence between cytogenetic and molecular responses is approximate. For example, some patients with *BCR-ABL1* transcript level > 1% may be in CCyR, whereas other patients with transcript levels ≤ 1% may not be in CCyR. Equally, relation between transcript level and number of leukemia cells is very approximate, partly because number of *BCR-ABL1* transcripts produced by individual leukemia cells may be very variable. Data adapted.[3,5,6]

Abbreviations: CCyR, complete cytogenetic response; CMR, complete molecular response; MCyR, major cytogenetic response; MMR, major molecular response; MR, molecular response; Ph, Philadelphia chromosome.

showed a modest (but significant) survival benefit for patients in CCyR who had achieved MR3 by 12 months compared with patients in CCyR but not in MR3. These data were not confirmed by a later analysis with longer follow-up of the same trial[13]; indeed, multiple other independent groups have failed to demonstrate additional benefit with regard to OS or PFS from achieving a response of MR3 or deeper at 12 or 18 months.[13-16] Although early achievement of deep MRs does not confer any survival benefit to patients, it is possible that later establishment of deep MRs could be a hallmark of optimal long-term outcome. In the report accompanying this article, Hehlmann et al[17] show that patients with CML who after 4 years of imatinib-based therapy were in MR4.5 (BCR-ABL^{IS} $<$ 0.0032%) had improved survival at 9 years (92% *v* 83%) compared with patients in a CCyR equivalent without deeper MRs (0.1% to 1%^{IS}). However, it is not clear how this new information can be incorporated into clinical practice. In this analysis, at 4 years, 7.3% of patients were in a molecular CCyR equivalent with no further response, 34.8% were in MR3 only (0.01% to 0.1%), 25.5% were in MR4 (but not MR4.5; 0.01% to 0.0032%), and 26.4% were in MR4.5 or higher ($<$ 0.0032%). Only this last group fared better than the 7.3% of patients in CCyR with no further MR. There was no significant difference in survival between patients who achieved MR4.5, MR4, or MR3. Finally, even if the correlation is valid, it does not prove that patients not achieving MR4.5 should be pushed indefinitely toward that goal.

As we have seen, there is large variability in the degree of MR that patients achieve with TKIs. The underlying biologic reasons for this variability have not been identified. Only Sokal score[15,18] and level of expression of hOCT-1[8,19,20] (ie, molecular pump that internalizes imatinib; not relevant for other TKIs) are robust prognostic factors for MR. It is likely that the variability in MR is related to differing levels of adherence to TKI therapy. Several groups have shown that adherence rate to imatinib is often poor and functions as a major prognostic factor for response.[8,21,22] For example, 25% of imatinib-treated patients with an adherence rate less than 90%

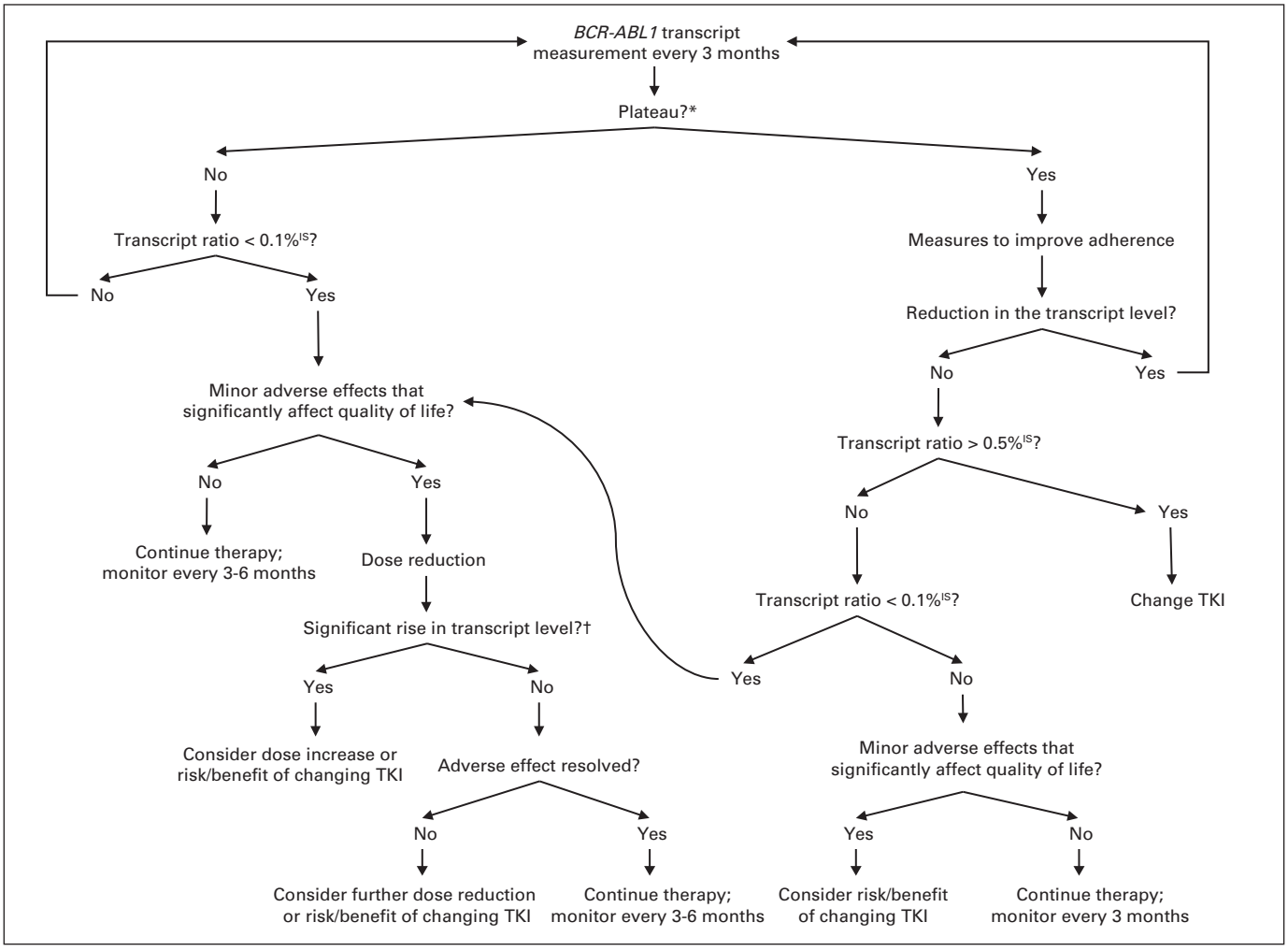

Fig 2. Algorithm for management of patients in complete cytogenetic response beyond 12 months of tyrosine kinase inhibitor (TKI) therapy. (*) It is difficult to define plateau, which essentially depends on two factors. One is intrinsic variability of quantitative polymerase chain reaction measurements. A physician has to become familiar with the degree of variation in transcript level that can be attributed to background noise in a given laboratory. It is important not to make decisions based on a single measurement. Second is duration of TKI therapy. Reduction in transcript level is typically fast at the beginning of therapy and slow after 3 to 4 years; for example, in the first year, one might expect a reduction of 2 to 3 logs, but in the second year, a reduction of only 0.5 to 1 log, and a decline after 4 years may be hardly perceptible. (†) Sometimes there is a modest (3 to 5×) rise in transcript level after reducing the TKI dose. This rise is usually (but not always) transient. For this reason, it is important to observe the patient for up to 6 to 9 months after having reduced the dose before making any clinical decision.

have a much lower probability of 6-year MR than adherent patients (MR3: 14% *v* 94% [$P < .001$]; MR4: 4% *v* 76% [$P < .001$]; CMR: 0% *v* 44% [$P = .002$]).[8] In a multivariable analysis including most of the biologic prognostic factors known to date, adherence was the only independent predictor for achievement of CMR.[8]

The French cooperative group reported in 2002 the outcomes of patients with CML who had obtained sustained CCyRs with interferon and then discontinued therapy. Seven patients, all in CMR, of 15 did not relapse.[23] This work was followed by a series of publications describing the experience of more than 100 patients who had discontinued imatinib after achieving CMRs,[9,10] defined as sustained CMR for at least 2 years with no detectable transcripts and a detection threshold corresponding to a 5-log reduction in *BCR-ABL1* transcripts. Using this definition, the 12-month probability of sustained CMR after imatinib discontinuation was 41%. Most of the MRs were seen during the first 6 months after discontinuation. High-risk Sokal group, female sex, and total imatinib therapy duration less than 50 months were independent predictors for MR.[10] Similar results have been reported by the same French investigators for patients who achieved CMRs while receiving dasatinib or nilotinib.[24,25] Using different CMR criteria, namely sustained MR4.5 for 2 years, the Australian group found that for patients in CMR who discontinued imatinib, the chance of sustained MR3 at 2 years was 47%.[26] Stopping treatment seems safe, because both studies showed excellent responses when TKIs had to be reintroduced. However, longer follow-up may be needed to fully ascertain the safety of stopping TKI therapy, because sudden blast crisis in patients in remission has been described post-transplantation[27] and after imatinib cessation, as reported in the accompanying article by Rousselot et al.[28]

In some patients deemed in remission after allogeneic stem-cell transplantation, *BCR-ABL1* transcripts can be consistently detected at levels higher than 0.0032%^{IS} (MR4.5) over prolonged periods of time without evidence of progressive disease.[29,30] This has two implications: First, it might be possible to discontinue or reduce the dose of TKIs in patients with detectable but stable low-level residual disease; it is hoped that trials will be designed in the future to explore these possibilities. Second, however, it is not clear at what transcript level TKIs should be reintroduced. In the companion report, Rousselot et al[28] describe the evolution of the *BCR-ABL1* transcript levels after stopping imatinib in 80 patients, but in this series, imatinib was only reintroduced if patients lost MR3. The 24-month cumulative incidence of loss of CMR was 54%, but the loss of MR3 was only 36%, clearly indicating that a substantial fraction of patients can have low levels of detectable disease without requiring clinical intervention.

SUGGESTED APPROACHES TO MANAGEMENT

Although the therapeutic targets for the first 12 months of TKI therapy are clear and based on solid evidence, namely $\leq 10\%^{IS}$ at 3 months and CCyR by 12 months (or earlier when patients are treated with nilotinib or dasatinib),[1,7,16,31-34] the situation is far less clear when managing patients in CCyR after 12 months of therapy. My current approach to the management of these patients is shown in Figure 2. I believe that patients in CCyR beyond 12 months should have a *BCR-ABL1* transcript ratio below 1%^{IS}, namely $< 0.5\%^{IS}$. However, I do not recommend any modification of therapy when MR3 is not achieved, because patients in CCyR with a 12-month transcript level $> 0.5\%^{IS}$ have an OS similar to that of patients who are not in CCyR, whereas patients with transcript levels $< 0.5\%^{IS}$ had an excellent OS irrespective of the degree of deeper MR.[16] It is unclear whether this recommendation is consistent with the findings reported by Hehlmann et al[17] in the companion article, because the cutoffs used to define the high-risk group were different (0.1% to 1%$^{\%\ IS}$ *v* $> 0.5\%^{IS}$). I do not believe that it is practical to aim for CMR (or MR4.5) as the main therapy target. First, it has no impact in OS or PFS. Second, and perhaps more important, only those patients who had adverse effects when receiving TKIs and who did not need to resume TKIs after discontinuation really benefited from having achieved CMR. Because this population is small, I do not feel that exposing patients to potentially more toxic (and certainly more expensive) drugs to achieve CMRs can be justified.

The principal reason why patients do not achieve deep MRs is poor adherence.[8] The patient in this case offers a good example of the difficulties that physicians face when trying to recognize poor adherence. The patient had many of the signals that suggest nonadherence. For example, the transcript level at 3 months was low, consistent with an excellent responder, but the rate of the leukemia burden decline

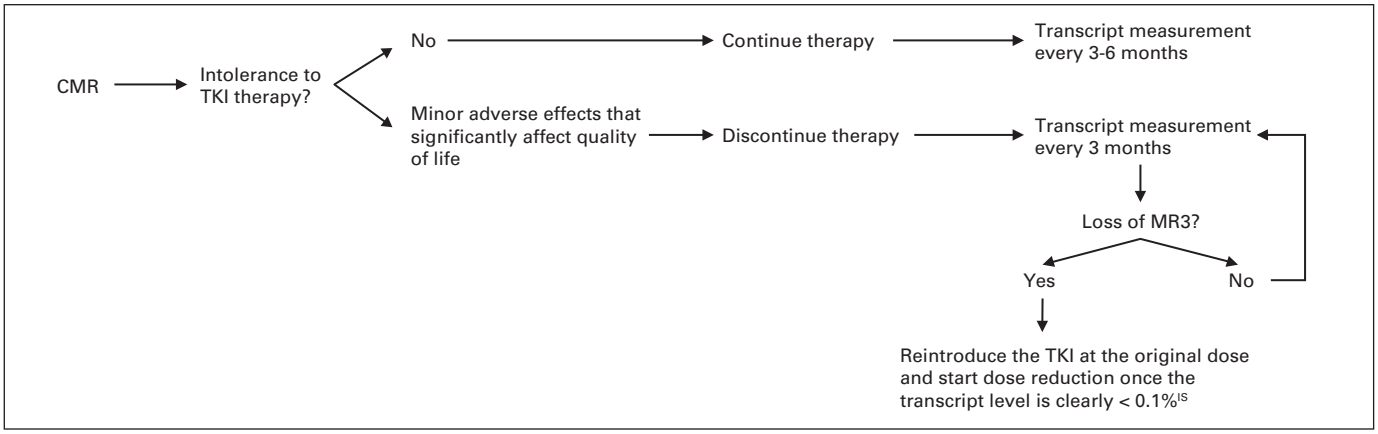

Fig 3. Algorithm for management of patients in stable complete molecular response (CMR). Definition of stable CMR that we use in Hammersmith Hospital is undetectable *BCR-ABL1* with an *ABL1* control > 40,000 transcripts for 2 consecutive years. MR, molecular response; TKI, tyrosine kinase inhibitor.

then reached a plateau. The patient also had unexplained but transient rises in transcript levels (Fig 1; July 2006), which are frequently seen in nonadherent patients. Finally, the patient had problems tolerating imatinib, which is often the reason for poor adherence.[8,35] Patients frequently do not share adherence habits with their clinical team,[36,37] which means that identifying patients who adhere poorly may be a major clinical challenge. In fact, on many occasions, the decision not to adhere results from a conscious decision by the patient to temporarily discontinue therapy for a number of reasons, the most common of which is to avoid persistent adverse effects (ie, asthenia).[35] For this reason, the first course of action with a patient who does not achieve an MR should involve maneuvers designed to improve adherence, regardless of what the patient states about his/her adherence and regardless of what the physician believes is happening at home. These maneuvers include education about the consequences of poor adherence, advice on techniques for improving adherence, psychological support, and most importantly better management of adverse effects, including dose reduction or change of therapy.

In the majority of patient cases, transcript levels do decline over time, and eventually, patients reach deep MRs (MR4 or better). For patients who tolerate their TKIs well, I do not recommend modifying or discontinuing therapy except in the setting of a clinical trial, because there is no potential clinical benefit, and the safety of other approaches is yet to be fully established. For patients, such as the one in this case, who experience low-grade adverse effects that significantly affect their quality of life, I recommend either a stepwise reduction in dose, leaving the minimal effective dose, or discontinuation of the TKI. There are no published data supporting the safety of a dose-reducing policy, although most physicians treating patients with CML routinely use this strategy. Dose reduction is my preferred approach for patients with adverse effects who achieve deep MRs but do not meet the stopping criteria of the French cooperative group. In this clinical case, imatinib was discontinued 18 months after the patient achieved MR4.5 and 6 months after he achieved CMR. The French and Australian groups both used 2 years in CMR (or MR4.5) as the criterion for discontinuation, but because neither shorter nor longer intervals have been studied, the optimal duration of CMR before attempting discontinuation remains unknown. Figure 3 shows my current approach to the management of patients in CMR.

The patient in this case achieved an MR 9 months after discontinuing imatinib. It would be reasonable, as supported by the companion report by Rousselot et al,[28] to watch and wait and reintroduce therapy only when (and if) the transcript level rises above MR3. But then what therapy should be chosen? One could reintroduce the same drug at the same or a reduced dose (the latter is probably more appropriate when treatment is reintroduced at a low transcript level); however, one could also resume treatment with an alternative TKI in the hope that the new drug would induce a deeper level of response, allowing the definitive discontinuation of treatment. To date, there is no clinical proof of the efficacy of this strategy.

For this case, I believe it is safe to defer reinstitution of any therapy, confident in the knowledge that if or when further treatment becomes necessary, it would almost certainly restore effective control of his leukemia. This dilemma for the modern physician stands in stark contrast to the clinical question that faced physicians in the preimatinib era, when the depressing challenge was to decide how best to manage a patient in blastic transformation.

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