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Perspective

Is a cure for CML without allogeneic stem cell transplantation around the corner?

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Before the advent of tyrosine kinase inhibitors (TKIs), chronic myelogenous leukemia (CML) was considered fatal or incurable without the use of allogeneic stem cell transplantation (SCT). However, the availability of TKIs since the year 2000 has allowed CML to be classified as a hematologic disease that does not require prompt allogeneic SCT and one that can be effectively controlled with TKIs as a life-long medication, similar to other chronic diseases, such as diabetes and hypertension that require life-long treatment.

TKIs induce durable responses and prolong the overall survival and progression-free survival of patients with CML in the chronic phase (CML-CP). Thus, allogeneic SCT is no longer recommended as a frontline treatment, not even in young patients with CML in the accelerated phase. As a result, allogeneic SCT is now only indicated for a selected patient group in whom the T315I mutation develops during TKI treatment or for patients who progress to blast crisis or fail to achieve the therapeutic goal after using 2 or 3 different TKIs.

In the IRIS study [1], the estimated overall survival of patients who received imatinib as the initial therapy was 89% at 5 years and 85% at 8 years (93% when considering only CML-related deaths). However, according to second-generation TKI studies, when used as frontline treatment, second-generation TKIs are able to achieve a superior molecular response or a higher rate of complete molecular/cytogenetic response than imatinib.

With a minimum follow-up duration of 3 years, the ENESTnd study compared nilotinib to imatinib in patients with newly diagnosed CML-CP [2]. The authors found that nilotinib was associated with a significantly lower probability of progression to the accelerated phase/blast crisis than imatinib (2 progressions [0.7%] with 300 mg nilotinib taken twice daily, 3 progressions [1.1%] with 400 mg nilotinib taken twice daily, and 12 progressions [4.2%] with imatinib). With regard to disease progression after discontinuing treatment, the advantage of nilotinib over imatinib in preventing progression remained significant (9 progressions [3.2%] with 300 mg nilotinib taken twice daily, 6 progressions [2.1%] with 400 mg nilotinib taken twice daily, and 19 progressions [6.7%] with imatinib). Nilotinib continues to demonstrate a superior efficacy in all key response and outcome parameters when compared with imatinib for the treatment of patients with newly diagnosed CML-CP.

In the phase 3 DASISION trial [3], patients with newly diagnosed CML-CP were randomized to receive either 100 mg dasatinib (N=259) or 400 mg imatinib (N=260) once daily. The cumulative response rates at 24 months in the dasatinib arm versus imatinib arm were as follows: complete cytogenetic response (CCyR), 86% versus 82%; major molecular response (MMR), 64% versus 46%; and *BCR-ABL* reduction to $\leq$0.0032% (4.5-log reduction), 17% versus 8%. Transformation to accelerated- or blast-phase CML occurred in 2.3% of patients treated with dasatinib versus 5.0% of those treated with imatinib. Thus, overall, dasatinib continues to show faster and more frequent responses than imatinib.

While the recent availability of multi-revolutionary drugs

has increased the hope of a cure for CML, drug cessation is also an essential factor for any real or operational cure. The key issues for drug cessation in CML are as follows: Which patient categories should be considered for drug discontinuation? What are the criteria for clinical or molecular relapse after the discontinuation of TKIs? Should the discontinuation of TKIs be attempted several times? Recent TKI discontinuation trials for CML patients who show an excellent response to therapy have already demonstrated the feasibility of successful TKI discontinuation for a subgroup of CML-CP patients. Moreover, the safe discontinuation of medication, either completely or for some time, is also a critical factor that affects not only disease progression, but also the patient's quality of life.

The criterion for TKI discontinuation is complete molecular remission (CMR) lasting for at least 2 years, and TKI discontinuation should only be considered within a clinical trial setting, under strict molecular monitoring. Only approximately 15% of patients taking imatinib and 35% of patients taking second-generation TKI achieve CMR at 2 years, thereby allowing them to be considered for discontinuation of medication.

In the prospective, multicenter, non-randomized Stop Imatinib (STIM) study [4], imatinib treatment (for >2 years) was discontinued in CML patients with CMR (>5-log reduction in *BCR-ABL* and ABL levels and undetectable transcripts on quantitative reverse transcription-polymerase chain reaction). Sixty-one percent of the patients relapsed (40 patients relapsed before 6 months, 1 in the 7th month, and 1 in the 19th month) after the cessation of imatinib. All patients who relapsed responded to the reintroduction of imatinib: 16 of the 42 patients who relapsed had decreased *BCR-ABL* levels and 26 achieved CMR that was sustained after the imatinib rechallenge.

Treatment-free remission (TFR) is an emergent concept for CML management. Thus, both TFR duration and the timing of retreatment in relapsing patients are important issues in drug discontinuation trials [5].

In the abovementioned STIM trial [4], relapse was defined as the reversion of the CMR status during TKI discontinuation. Thus, when analyzing published data on TKI discontinuation, the definition of relapse should also be considered. Indeed, recent discontinuation trials recommend retreatment with the same TKI in the event of a reversed MMR status [5-7].

In a trial with nilotinib as the frontline treatment, and in which relapse was defined as a reversed MMR status, the TFR rate reached 70% [5]. The chances of achieving CMR and acquiring TFR were approximately 2 times higher in CML patients taking second-generation TKIs than in patients taking imatinib [5].

When attempting TKI discontinuation for a second time in CML patients with a second sustained CMR, most, but not all, patients had a molecular relapse [6, 8]. This suggests that TKI discontinuation can be attempted several times, although further studies are needed to evaluate the impact of multiple discontinuation attempts.

These studies notwithstanding, drug discontinuation trials still raise certain concerns. Theoretically, the possibility of acquiring resistance to TKIs, or the sudden development of a blast crisis should be taken into account when attempting drug cessation in patients with CML. The current recommendation is for CML patients to continue treatment indefinitely, as the ability of TKIs to eradicate the CML clone is still uncertain. Thus, drug discontinuation can only be attempted in a clinical study setting with patient groups that demonstrate stable CMR after long-term medication.

Residual disease has been shown to be enriched within the stem cell compartment and to persist at stable levels for up to 5 years with a CCyR. This finding has led to searches for novel strategies to eliminate these stem cells, and such strategies may be essential for achieving a cure. As a result, the alternatives to long-term TKI therapy that are currently being explored to eradicate minimal residual disease include investigational treatment regimens that incorporate interferon, hydroxychloroquine, BCL6 inhibitors, the smoothened antagonists LDF225 and BMS-833923, and a combination of TKIs and new drugs [9].

Accordingly, achieving a cure for CML-CP without the use of allogeneic SCT would seem to be realistically imminent, given the development of more powerful therapeutic agents and significant advances in CML treatment [7].

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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