Challenges for monitoring patients in emerging economic regions

Monitoring response to tyrosine kinase inhibitor therapy is now an important component of patient management and BCR-ABL1 transcript levels can dictate a change of treatment. The test is performed on peripheral blood at a relatively small cost compared with the overall cost of drug therapy. Most patients have a successful outcome and their response can be tracked as an initial rapid decline in BCR-ABL1 transcripts followed by a very slow decline over many years that culminates in a deep molecular response, which is associated with long term optimal outcome. A rise in BCR-ABL1 can signal the onset of resistance and loss of response, in which case BCR-ABL1 mutation analysis is warranted. A rise can also accompany nonadherence to the prescribed dose of tyrosine kinase inhibitor, which is a warning that long term response may be less than optimal.

Molecular monitoring in some countries would be considered optimal: standardised to the international reporting scale, available to all patients through government subsidy or at a low cost, and available at the appropriate frequency. The frequency of testing changes over the course of therapy and according to treatment response. More frequent monitoring in the initial months is important to assess the trend of response and the response level. BCR-ABL1 values that remain >10% on the international scale at 3 and 6 months are associated with poorer long term outcomes and signal treatment failure, which mandates a change of therapy to reduce the risk of disease progression. Reaching a major molecular response (≤ 0.1%) at 12 months is considered optimal and continuation of the current therapy is advised. More frequent molecular monitoring is required in case of less than optimal response or if drug resistance is suspected. More frequent monitoring may also be required many years after commencing therapy to track a deep molecular response, which is a prerequisite for a trial of drug cessation. Patients with a sustained deep response may be candidates for treatment free remission. The most critical time for molecular recurrence after drug cessation is within the first 6 months of stopping, and monthly monitoring is important to allow rapid drug restart upon molecular recurrence.

Although an increasingly integral factor for optimal outcomes, molecular monitoring is not available to all patients at the required frequency, or indeed may not be available at all due to lack of testing capacity or prohibitive cost to the patient. The iCMLf and the Max Foundation aim to improve access to molecular monitoring in low resource regions, such as the Philippines where in 2010 no molecular testing was available and patients had never been monitored despite having had CML for years. To this end, some high resource countries through the iCMLf and Max Foundation were able to offer molecular testing to a few patients who were otherwise denied monitoring, many of whom were suspected of having drug resistance. In the Philippines a concerned father of a young boy with CML coordinated the first monitoring for 30 patients from Manilla where frozen blood samples were sent to Adelaide, Australia for testing. Approximately 40% of patients had BCR-ABL1 resistant mutations and advice was offered for the appropriate TKI for rescue of response based on the mutation resistance profile. Frozen blood shipment is very expensive, but recent studies performed in Seattle have demonstrated that blood spotted onto a paper template and posted via standard mail generates reliable BCR-ABL1 values at a substantially reduced cost.

For improved outcomes for patients in low resource countries, point of care molecular monitoring is needed and efforts towards standardised protocols have improved the reliability of results, although most methods require expensive machinery and high technical skill and training. An alternative is the Cepheid GeneXpert analyser where all of

the processes required to generate a quantitative BCR-ABL1 value is contained within a microfluidic cartridge and requires low technical skill. Many centres have acquired the instrument through agreements with the Max Foundation and can now offer patient monitoring.

An unmet need for all patients is appropriate prediction and effective intervention for those with primary drug resistance or early disease transformation. The next generation of sequencing technology is starting to identify genomic lesions in addition to BCR-ABL1 that may impact treatment outcome. A greater understanding of the mechanisms driving poor outcome will lead to improved treatment options and outcomes. Our understanding of CML is far from complete and although tremendous advances have been made for the majority of patients, future research and greater access to fundamental monitoring should lead to improved outcomes for more patients and potentially increase the number of patients able to achieve treatment free remission.

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