Chronic myeloid leukemia: The race is yet to be won

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I do not run marathons, but I have been around those who do enough to hear them talk about hitting "the wall." After about 20 miles, many runners reach a point at which further progress seems impossible, and they start to question whether they will be able to complete the race. In many ways, I feel as though we have hit the wall in our understanding of chronic myeloid leukemia.

The past half century has been an extraordinary run that has us on an excellent pace to not only complete the race to a cure, but to do so in record time. One need only look at the change in the natural history of the disease that has occurred during this time to understand the speed of our progress: in the 1960s, median survival was three to five years; today, the expected survival at 5 years is 90%.[1] This change is unparalleled in oncology.

Despite this progress, many challenges remain that merit a concerted effort from researchers, health care providers, regulatory authorities, third party payers and the patients themselves. Our goal should be to eliminate the disease in all patients. With this objective, the results achieved with imatinib, remarkable as they are, should not satisfy us as being complete.

From the initial studies with imatinib, we know that only about 60% of patients have an acceptable outcome.[2] Only about 80% of patients achieve a complete cytogenetic response with imatinib, and about 15% of them will eventually lose this response. An additional 4%–8% have an intolerance to imatinib. Thus, nearly 40% of patients have an unacceptable outcome with imatinib.[2] Although we have developed excellent second-line treatments with agents such as dasatinib and nilotinib, only about 50% of patients who have a resistance to imatinib achieve a complete cytogenetic response with these agents, and at least 10%–15% will eventually lose their response.[3,4]

If we are to achieve the ultimate goal of eliminating this disease in all patients, we must change our focus in several ways. First, we must change the perception that patients do very well with imatinib therapy; although many of them do, too many do not. Thus, it is important to maintain our focus on long-term goals. Patients who do not have an optimal response to treatment may feel good, and their physical examination and results of blood tests frequently appear normal. However, a patient with residual disease is unlikely to remain alive and well in later years.

The management of patient care has become much less challenging than in the days of interferon therapy, considering the relatively low toxicity of tyrosine kinase inhibitors and the high rate of response to treatment. These factors could lead to relaxed adherence to monitoring requirements. A patient needs to be followed properly, with close attention paid not only to the response parameters (with cytogenetic and molecular assessments at periodic intervals), but to the management of any adverse events the patient may experience. Understanding and managing these common, relatively minor adverse events is another area in which we could improve.

Patients receiving continual treatment for chronic myeloid leukemia experience what we term low-grade adverse events (e.g., fatigue, gastrointestinal symptoms, muscle cramps, skin toxicity). There are also long-term consequences to the administration of tyrosine kinase inhibitors. Growth retardation is well described in children. There is debate over the possible effects that continuous treatment may have on bone metabolism. Furthermore, with an increasing number of young patients with this disease, pregnancy is a common issue. Despite the case reports and series reporting the outcome of patients who become pregnant, there is little research on the optimal management of the disease in these patients, and current recommendations are based more on anecdotes and extrapolations than on actual data.

Recently, newer tyrosine kinase inhibitors (such as dasatinib and nilotinib) have been used for initial treatment of the disease. The results have been excellent and have led us to conclude that these agents are better options for initial treat-

Key points

- The progress we have made in understanding the biology and management of chronic myeloid leukemia is unprecedented in oncology.
- Second-generation drugs have successfully treated the disease in patients with resistance or intolerance to imatinib, but fewer than half of such patients have a favourable long-term outcome.
- The common current perception is that chronic myeloid leukemia has been conquered, but unless we pay attention to the remaining unmet needs of patients, we will fail in our quest for a cure.

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ment.[5,6] Still, the cost and availability of these drugs mean that using them to start treatment in all patients may not be desirable. The studies to date have been designed to determine which is the better drug, but these studies have multiple limitations. Capricious heterogeneity in the definition of outcomes (event-free survival, progression-free survival, etc.) has made the objective evaluation of data difficult for the treating physician.[7] Furthermore, these studies are handicapped by the censoring of patients and the limitations in following patients after they leave the study, which prevents us from knowing their true long-term outcomes. In addition, the design of these studies is such that it compares imatinib with new tyrosine kinase inhibitors; when an event occurs, the opposing drug "scores a point." This design does not account for the way care is managed when imatinib is used for initial treatment and the response or tolerance is inadequate, leading to patients receiving one of the newer drugs.[8] We have focused on the benefits of one drug versus another, instead of looking at a more effective strategy (e.g., to change treatment after imatinib fails or when a slow response is seen). Finally, the newer drugs have not been compared head to head; regrettably, this may never happen.

Soon after the introduction of imatinib, the remarkable discovery of mutations in the *ABL* kinase domain in patients who developed resistance helped us better understand how tyrosine kinase inhibitors work and led to the development of new molecules that could overcome certain mechanisms of resistance. Mutations are indeed associated with resistance to imatinib in about 50%–60% of all patients. However, resistance to tyrosine kinase inhibitors is a complex phenomenon that is probably multifactorial in most patients. We have been so enamored with the discovery of the *ABL* mutation that we have paid little attention to other possible mechanisms.

A cause of less-than-ideal responses is lack of adherence to treatment. Even when considering only those who have achieved a complete cytogenetic response, an alarming 20% of patients miss at least 10% of their doses of imatinib.[9] Reasons for missed doses include persistent "mild" adverse events, finances and a lack of understanding of both the goals of treatment and the consequences of silent recurrence or persistence of the disease.

Adequate follow-up, managing adverse events and educating our patients as to the goals of treatment and the realities of persistent disease are all helpful in combating lack of adherence. However, we should also find ways to make treatment finite. Certainly, if we could cure or control other cancers with an oral medication taken once or twice daily, we would be very pleased; however our accomplishments or lack thereof in the treatment of other cancers is not the point. Our focus should be what we have accomplished in the treatment of chronic myeloid leukemia and what further improvements we can make. Fortunately, this goal has captured the interest of researchers. Although a few patients may discontinue therapy without recurrence, this occurs only among those patients with a sustained complete molecular response for at least two years, and only about 40% of these patients remain in complete remission after treatment has been interrupted.[10] Therefore, current treatment recommendations are unchanged; the research in this area and its application needs to be done responsibly and in such a way that the long-term interests of patients are protected.

This is no time to quit our marathon. We are almost at its end; we must maintain our focus, take advantage of our training and make a run for the finish line. More research is needed. We require new drugs, available to all patients, to replace the existing agents when they do not work well enough. Until all patients with chronic myeloid leukemia can have an optimal quality of life while fighting this disease, our marathon is not over.

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