Two recent publications have highlighted the remarkably improved outcomes of patients with chronic myelogenous leukemia (CML) who have been treated in the era of tyrosine kinase inhibitors (TKIs). The first was a single-institution study of CML patients receiving imatinib after interferon failure, reaffirming good long-term prognosis (Cancer. 2012;118:3116-3122). Hagop Kantarjian, MD, professor of medicine, and colleagues identified 368 adult patients with CML in the chronic phase who were treated with imatinib at The University of Texas MD Anderson Cancer Center (MDACC) in Houston after failing interferon therapy. The authors explained that a single-institution study might be better than multiinstitutional or pharmaceutical-sponsored trials for long-term follow-up after patients are taken off protocol. The median follow-up of the patients was 114 months. Overall, 247 patients (67%) had a complete cytogenetic response (CCyR). Of the 326 patients who had molecular studies, 207 (63%) achieved a major molecular response (MMR). In an intent-to-treat analysis of the entire group of 368 patients at 7 years, 129 patients (35%) were in CCyR, 116 (32%) were in MMR, and 40 (11%) had undetectable BCR-ABL levels on molecular testing. (For a detailed explanation of response criteria in CML, see the National Comprehensive Cancer Network Clinical Practice Guidelines for CML, available at NCCN.org.)

The 10-year estimated survival rate was 68%, with a progression-free survival rate of 67%. The authors compared this with a 10-year survival rate of 20% to 30% reported in a group of similar patients before the availability of imatinib. In all, 127 patients failed therapy with imatinib: 86 remained in chronic phase and 41 patients experienced transformation. Sixty-two of the 127 patients who failed received a second-generation TKI and the estimated 5-year survival rate from the time of salvage TKI was 60%. "While the outcomes are favorable for continued imatinib therapy, we have to continue to investigate approaches for cure. For patients with minimal residual disease, we need to find out what drugs can be added, either existing or novel agents, that may be curative and allow therapy to be stopped," says Dr. Kantarjian.

Multivariate analysis identified several adverse prognostic factors: age ≥ 60 years, hemoglobin level < 10 g/dL, the presence of any blasts on the peripheral smear, bone marrow basophils > 5%, and clonal evolution at the start of imatinib therapy. Long-term outcomes were found to be significantly improved in patients achieving either a major cytogenetic response (hazard ratio [HR], 0.12; P < .001) or a complete hematologic or minor cytogenetic response (HR, 0.36; P = .003) within 12 months of the initiation of imatinib. "In the past, the treatment of CML was centered on bone marrow transplantation, which was effective, but only done at specialized centers. With the advent of tyrosine kinase inhibitor therapy, a shift into community practices is occurring," says Jerald Radich, MD, associate professor of medical oncology at the University of Washington School of Medicine in Seattle. He believes the take-home message is that general oncologists will see more patients with CML and need to stay educated about optimal management.

Increasing Prevalence
Recognizing that the median survival of individuals with CML was 3 years to 6 years before the use of imatinib, a second study analyzed how the lengthened life span of patients with CML would ultimately affect the prevalence of disease. Xuelin Huang, PhD, and colleagues...
demonstrated that, based on current data, the number of individuals living with CML will continue to increase and eventually reach a prevalence that is approximately 35 times the annual incidence of disease (Cancer. 2012;118:3123-3127). “The strength of our study was the use of solid and sensible mathematical and statistical methods, and a weakness was the fact that we could not take into account probable future treatment improvements which may also affect prevalence,” says Dr. Huang, associate professor in the department of quantitative sciences at MDACC.

The authors state that the annual incidence of CML has been consistent, with 4800 to 5200 new cases diagnosed each year in the United States. The mortality rate before the availability of imatinib was 10% for the first 2 years after diagnosis and 20% to 25% for subsequent years. However, this has been reduced to a mortality rate of about 2% per year for the first 10 years of follow-up. The authors aimed to calculate the increased prevalence of CML and where it would plateau. To make this calculation, they used several factors derived from a review of the literature: the annual mortality rate of patients with CML who are treated with imatinib, the incidence of CML, and the estimated aging and growth of the US population.

The all-cause mortality rate of patients with CML who receive imatinib is 1% to 2% in the first 8 years to 10 years from diagnosis. This is based on a patient population with a median age of 40 years to 50 years. However, as a patient ages, the all-cause mortality increases. Therefore, investigators compared the mortality rate of a cohort of newly diagnosed patients with CML with a general population cohort with the same age distribution. An HR (or mortality ratio) of 1.53 was calculated using a Cox proportional hazards model. This ratio, along with the published incidence of CML and census information, was used to calculate disease prevalence.

The researchers’ analysis projected that the number of patients in the United States with CML would be 70,000 in 2010, 112,000 in 2020, 144,000 in 2030, 167,000 in 2040, and 181,000 in 2050. They projected that by 2050 the prevalence will have plateaued.

Furthermore, assuming that the mortality ratio remained constant, researchers estimate that the median remaining lifetime for a newly diagnosed patient with CML is approximately 22 years.

Practice Implications

The authors explain that this analysis may help in planning future clinical trials and aid in understanding and planning for the economic impact of CML. For the most part, patients need to remain on TKIs for disease control because it is more of a functional than actual cure. CML has essentially changed into a chronic condition such as diabetes or hypertension, with patients requiring long-term management. “Even primary care providers will have CML patients on tyrosine kinase inhibitors as part of their practice, and therefore must be familiar with [the management of these patients],” says Dr Radich. The economic implications of continued therapy and an increasing disease prevalence may pose a challenge as well. “Currently, the second-generation tyrosine kinase inhibitors are better when looking at early endpoints, but an increase in overall survival is not yet shown,” says Dr Kantarjian. “If we do find an overall survival benefit, as a society we will be faced with a decision regarding what cost-benefit ratio we will accept and can afford, as when imatinib is generic in the next couple years the cost will be many times less than the second-generation TKIs,” he says.

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