Chronic Myeloid Leukemia Beyond 2016 – Some Important Questions

Imatinib mesylate and other BCR-ABL selective tyrosine kinase inhibitors (TKIs) have dramatically changed the treatment algorithm and prognosis of Philadelphia chromosome-positive chronic myeloid leukemia (CML) (1-8). With these therapies, the annual mortality in CML has been reduced from a historical rate of 10% in the first 2 years and 15 to 20% subsequently to a CML-causal annual mortality rate of 1%. When treated appropriately and compliantly, and monitored for early signs of resistance, patients with CML have an expected 15-year survival rate of 85%, not different with imatinib and second generation TKIs, because of the availability of highly effective salvage therapies among patients identified early to have cytogenetic relapse and treated appropriately. Today, imatinib, nilotinib and dasatinib are approved for frontline therapy (4, 5). Among patients with CML resistance or treatment intolerance, nilotinib, dasatinib and bosutinib are potential salvage therapies depending on prior exposure, co-morbid conditions, and identification of CML resistant mutations. Ponatinib, a third generation TKI selectively effective against T315 I mutations, and highly effective generally across other mutations, is also useful as subsequent salvage therapy (9, 10). Long-term side effects are emerging with TKIs that require proper management. These include renal dysfunction; rare neuro-toxicities misdiagnosed as Alzheimer's disease, dementia or Parkinsonism, and which can be reversible with treatment interruption; vaso-spastic conditions including myocardial insufficiency and infarct, transient cerebral ischemic attacks or cerebr0-vascular accidents, peripheral arterial disease; systemic and pulmonary hypertension; worsening of diabetes; rare pancreatitis, etc.

Multiple questions remain as to optimal treatment and monitoring of CML.
These include:

1. The role of frontline therapy with generic imatinib versus second TKIs. Perhaps second TKIs could be reserved as first-year of therapy to reduce the incidence of transformation in general, followed by imatinib therapy once patients achieve cytogenetic CR. Alternatively should second TKIs be used in high-risk CML and in younger patients (e.g. age younger than 50 to 60 years) to induce higher rates of durable complete molecular responses (CMR) which may help improve the rates of TKI treatment discontinuation (a more important consideration among younger patients). This raises the question of the cost-benefit of second TKIs: how much should we pay for TKIs for the treatment of the total population in order to allow for a differential treatment discontinuation and differential molecular cure rates of 5 to 10%?

2. Can we improve the rates of durable CMRs and potential molecular cures and what are potential optimal strategies (e.g. pegylated interferon, checkpoint inhibitors, BCL-2 inhibitors, JAK-2 inhibitors, etc.)?
3. What is the optimal management of CML in transformation? Can we develop better definitions of CML accelerated phase (e.g. high percent of blasts and basophils, selective cytogenetic abnormalities including isochromosome 17 and 3q26.2 rearrangements)?
4. What is an optimal treatment monitoring and timing interventions? Is the aim of therapy achievement of complete cytogenetic response or deeper molecular responses? Should we consider a change of TKI therapy based on BCR-ABL transcript levels (International Standard) of >10% at 3 or 6 months into frontline therapy? Is cytogenetic CR necessary for older patients who become resistant to multiple TKIs or can they maintain durable chronic phase disease with lesser degrees of cytogenetic response? Should BCR-ABL mutations detection be performed with more sensitive next generation sequencing (versus the current Sanger sequencing) as the new standard of care?
5. What is the optimal role and timing of allogeneic stem cell transplant (SCT) in advanced nations (where the cost of long-term TKI therapy is less relevant) versus emerging nations (where SCT could be a one-time curative treatment with a cost of less than $20,000).
6. Treatment interruption of TKIs among patients with durable CMR. Management of women with CML on TKIs in relation to pregnancy.
7. What are the dose-schedule ranges of each of the TKIs that allow continued benefit from equal efficacy and reduce toxicities? For example ,is the approved dose of ponatinib 45 mg daily the best dose, or are daily doses of 30 mg or 15 mg appropriate depending on response status and side-effects or co-morbid conditions?

   These above questions and other important ones related to optimal CML management and monitoring will be discussed.

Hagop M. Kantarjian, M.D.

MD Anderson Cancer Center

University of Texas, Houston, USA

References

1. Kantarjian H, Sawyers C, Hochhaus A, Guilhot F, Schiffer C, Gambacorti-Passerini C, Niederwieser D, Resta D, Capdeville R, Zoellner U, Talpaz M, Druker B. Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. N Engl J Med 346(9):645-52, 2/2002.
2. Kantarjian H, Giles F, Wunderle L, Bhalla K, O'Brien S, Wassmann B, Tanaka C, Manley P, Rae P, Mietlowski W, Bochinski K, Hochhaus A, Griffin JD, Hoelzer D, Albitar M, Dugan M, Cortes J, Alland L, Ottmann OG. Nilotinib in imatinib-resistant CML and Philadelphia chromosome-positive ALL. N Engl J Med 354(24):2542-51, 6/2006
3. Kantarjian H, Shah NP, Hochhaus A, Cortes J, Shah S, Ayala M, Moiraghi B, Shen Z, Mayer J, Pasquini R, Nakamae H, Huguet F, Boqué C, Chuah C, Bleickardt E, Bradley-Garelik MB, Zhu C, Szatrowski T, Shapiro D, Baccarani M. Dasatinib versus Imatinib in Newly Diagnosed Chronic-Phase Chronic Myeloid Leukemia. N Engl J Med 362(24):2260-70, 6/2010. e-Pub 6/2010.
4. Saglio G, Kim DW, Issaragrisil S, le Coutre P, Etienne G, Lobo C, Pasquini R, Clark RE, Hochhaus A, Hughes TP, Gallagher N, Hoenekopp A, Dong M, Haque A, Larson RA, Kantarjian HM. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med 362(24):2251-9, 6/2010. e-Pub 6/2010.
5. Cortes JE, Kim DW, Pinilla-Ibarz J, le Coutre P, Paquette R, Chuah C, Nicolini FE, Apperley JF, Khoury HJ, Talpaz M, DiPersio J, DeAngel DJ, Abruzzese E, Rea D, Baccarani M, Muller MC, Gambacorti-Passerini C, Wong S, Lustgarten S, Rivera VM, Clackson T, Turner CD, Haluska FG, Guilhot F, Deininger MW, Hochhaus A, Hughes T, Goldman JM, Shah NP, Kantarjian H; PACE Investigators. A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. N Engl J. Med. 369(19): 1783-96; 11/2013.