Chronic myeloid leukemia 2018 update on diagnosis, therapy and monitoring

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Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm with an incidence of 1-2 cases per 100 000 adults. CML is characterized by a genetic translocation, t(9;22)(q34;q11.2), this rearrangement is known as the Philadelphia chromosome. The molecular consequence of this translocation is the generation of a BCR-ABL1 fusion oncogene, which in turn translates into a BCR-ABL1 oncoprotein.

Frontline therapy: Four tyrosine kinase inhibitors (TKIs), imatinib, nilotinib, dasatinib, and bosutinib are approved by the United FDA as first-line treatment of patients with newly diagnosed CML in chronic phase (CML-CP). Clinical trials with second generation TKIs reported significantly deeper and faster responses but this has not translated into improved long-term survival, because of the availability of effective salvage therapies .Patients who develop the T315I mutation display resistance to all currently available TKIs except ponatinib.

Treatment-free remission (TFR) has recently emerged as a goal of treatment in chronic myeloid leukaemia.The minimum eligibility criteria for a trial of TFR are not yet defined, but the available data support a MRD level of around a molecular response of 4·5 log for at least 2 years. Factors associated with a higher probability of TFR include low risk Sokal score, prior interferon treatment, longer total duration of imatinib treatment and higher numbers of natural killer cells at the time of imatinib discontinuation. Preliminary data suggest that the rate of TFR in patients treated with more potent tyrosine kinase inhibitors will probably be higher. The biology that underlies TFR is an area of active investigation.

The FDA's December 2017 Tasigna update, however, has some encouraging news for CML patients. The label now stipulates that Ph+ CML patients in the chronic phase may qualify to stop treatment with Tasigna altogether. However, you must take Tasigna for at least three years and achieve specific predetermined remission criteria before stopping treatment. More specifically, the updated FDA guidelines say patients must achieve a sustained deep molecular response of MR4.5 before stopping Tasigna sustained deep molecular response of MR4.5 before stopping nilotinib . The FDA also recently authorized a test that can detect this response in nilotinib therapy patients that achieve treatment-free remission.

Allogeneic stem cell transplantation although remains an important therapeutic option for patients with CML-CP who have failed at least 2 TKIs, and for all patients in CML advanced phases.

Earlier this year, Bin Zhang, MD, PhD, Associate Research Professor in the Department of Hematologic Malignancies Translational Science at City of Hope led a study published in *Nature Medicine* on a more effective, less toxic treatment for patients with CML involving miristen—a new drug developed at the facility—and TKIs (2018;24:450-462). We have reason to believe miristen makes TKIs more effective at killing the leukemia stem cells, so we treated mice with CML with different drug combinations and found those treated with miristen and TKI who had received stem cell transplants went into complete remission.

Miristen targets a type of microRNA that is expressed in leukemia stem cells, known as miR-126. We believe this RNA molecule plays an important role in the self-renewal and persistence of cancer-causing leukemia stem cells. By eliminating this molecule in the blood, there›s an opportunity to reduce the chance of cancer recurrence by eradicating the stubborn stem cells altogether.

Transplantation of the bone marrow cells collected from those treated with miristen and TKI resulted in no sign of leukemia in the healthy recipient mice, meaning all leukemia stem cells were eliminated.