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NCCN and ELN: What do the guidelines tell us?

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A B S T R A C T

The prognosis for patients with Chronic Myeloid Leukemia is vastly different in 2016 compared to 20 years ago, and this is due to the development of BCR-ABL tyrosine kinase inhibitors (TKIs). As newer, more potent, TKIs have been developed and approved over the past 15 years, the decision about which drug to use as first line therapy, and when to switch treatment in particular patients has become more complicated. The National Comprehensive Cancer Network (NCCN) and the European LeukemiaNet (ELN) have developed treatment and monitoring guidelines to aide in the management of these patients. The guidelines were developed by two groups of CML experts and recommendations are based on available data and expert opinion. With adherence to the recommendations proposed by the NCCN and ELN, we can expect to continue to see excellent outcomes for our patients with CML.

Overview

Expected outcomes for patients with Chronic Myeloid Leukemia are vastly different in 2016 compared to what they were in the 1990's and early 2000's. Whereas previously responses to CML directed therapy were assessed on a hematologic and cytogenetic level, in the current era of highly effective BCR-ABL tyrosine kinase inhibitors successful treatment responses are assessed using sensitive molecular testing methods including quantitative polymerase chain reaction (Q-PCR) to quantify BCR-ABL transcript levels.

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The National Comprehensive Cancer Network (NCCN) and the European LeukemiaNet (ELN) are two of the predominate international committees which have designed evidence based guidelines for the treatment and management of CML in chronic (CP), accelerated (AP) and blast (BP) phases of the disease. The NCCN CML committee is comprised of a group of CML experts from each of the 26 NCCN Member Institutions. The guidelines are evidence based and result from the author's analysis of published data as well as their views of currently accepted treatment approaches.

The ELN CML panel is made up of 32 experts from Europe, America and the Asian-Pacific region who have come together on multiple occasions to discuss pertinent questions related to the most up-to-date literature regarding management of CML. Their recommendations are the result of consensus from the entire group in regard to the most evidence based treatment and management of CML.

Here we discuss the NCCN and ELN guidelines for all phases of CML as well as some of the data that has been analyzed in order to develop these recommendations.

Diagnosis and first line treatment

Both the ELN and the NCCN recommend a complete workup at the time of diagnosis including a history and physical with accurate measurement of the patient's spleen. A complete blood count with a differential along with a bone marrow biopsy and aspirate to determine the blast and basophil percentage are essential components for determining the phase of CML. G-banding cytogenetics and QPCR to measure BCR-ABL transcripts reported on the International Scale are also necessary at the time of diagnosis. This baseline information is needed in order to determine a patient's risk score which could be done using the Sokal or Hasford Score per the NCCN guidelines, or the Sokal, Euro or EUTOS score per the ELN guidelines [1,2].

All of the above data should be analyzed together in order to choose the most appropriate first line treatment for a patient. In 2016, all available CML treatment recommendations suggest that first line therapy should be a BCR-ABL tyrosine kinase inhibitor, with very few exceptions. Currently, there are three TKIs approved in the first line setting including imatinib (first generation), dasatinib and nilotinib (second generation) [3–5]. Neither the ENL nor the NCCN specifically recommend one TKI over the other, however the NCCN guidelines suggest that those with intermediate- or high-risk Sokal or Hasford scores may fare better with a second generation TKI rather than imatinib [1].

The IRIS Study showed a significant increase in cytogenetic response rates in imatinib treated patients compared with those receiving Interferon and low-dose Cytarabine [3], however due to the high rate of cross-over from IFN to imatinib, the study results did not show a survival benefit after 1 year [6]. A significant survival benefit was demonstrated with imatinib when compared with historical controls who were treated with IFN [7]. Long-term data from the IRIS trial indicate a CCyR rate of 82% with a median follow-up of 60 months with only 7% of patients progressing to AP or BP CML. At the same time period the overall survival (OS) was 89% [8].

Dasatinib 100 mg once daily was compared with imatinib 400 mg once daily in 519 newly diagnosed CML patients in the DASISION trial and after a minimum follow-up of 12 months, the confirmed rates of CCyR and MMR were higher in the dasatinib arm compared with the imatinib arm (CCyR 77% vs. 66% and MMR 46% vs. 28%). The safety and tolerability was similar between both drugs [4]. With 5-years of follow-up, dasatinib has demonstrated faster and deeper cytogenetic and molecular responses compared with imatinib. Dasatinib also resulted in higher rates of CCyR (83% vs. 78%; $p = 0.187$), MMR (76% vs. 64%; $p = 0.002$) and $MR^{4.5}$ (42% vs. 33%; $p = 0.025$) at 5 years. Furthermore, progression to AP/BP CML were lower in dasatinib treated patients (4.6% vs. 7.3%) [9]. When stratifying patients based on Hasford score, dasatinib induced more MMRs than imatinib in each risk group (low 73% vs. 56%; intermediate 61% vs. 50%; high 57% vs. 38%) [9].

Nilotinib 300 mg twice daily and nilotinib 400 mg twice daily were compared to imatinib 400 mg daily in newly diagnosed CML patients in the ENESTnd trial. The 12-month analysis indicated higher rates of CCyR and MMR in nilotinib treated patients. CCyR was achieved at 12 months in 80%, 78% and 65% of nilotinib 300 mg, nilotinib 400 mg and imatinib patients respectively. MMR was achieved at 12 months in 44%, 43% and 22% of nilotinib 300 mg, nilotinib 400 mg and imatinib patients respectively. These superior CCyR and MMR rates were seen with nilotinib across all Sokal risk groups. Moreover, the rate of transformation to advanced phase CML was 4% in the imatinib arm compared with <1% in either