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Update of recent studies in chronic myeloid leukemia

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The use of tyrosine kinase inhibitors (TKIs) has dramatically improved outcomes for patients with chronic myeloid leukemia (CML). The IRIS study is the definitive phase III trial of imatinib mesylate as frontline therapy for CML. Seven year follow-up data has recently been reported [1]. The overall survival (including deaths from all causes) is 86% and the event free survival is 81% at seven years. Seven percent of patients have progressed to accelerated or blastic phase, with the highest risk being in the second year of treatment. Eighty-two percent of patients have achieved complete cytogenetic remission (CCyR) and 83% of these patients maintain that remission. Of the patients that discontinued study, 8% were for toxicity, 15% for efficacy and 17% for other reasons.

In the United States, the FDA approved dose of imatinib for patients in chronic phase is 400 mg daily. However in the original phase I study a true MTD was not determined, and the 400 mg dose was chosen because it was biologically active. More recent data suggests that higher doses may be more efficacious. In the TOPS Trial newly diagnosed patients received either 400 or 800 mg imatinib as front line therapy [2]. The primary endpoint of the study, major molecular remission (MMR) at 12 months, was similar in the two arms. However patients receiving imatinib 800 mg daily achieved complete molecular remission (CMR) faster (8.4 months versus 13.6 months, respectively, p = 0.0038) than patients receiving 400 mg of imatinib daily. The Central European Leukemia Study Group performed a similar study, the ISTAHIT study, in which previously treated patients (with agents other than TKIs) received imatinib 800 mg daily versus 400 mg daily for the first 6 months of therapy [3]. After that all patients received 400 mg daily. This study demonstrated that patients receiving imatinib 800 mg achieved a MMR and/or CCyR faster than patients receiving imatinib 400 mg. Another study of high dose versus standard dose imatinib failed to show a statistically significant increase in the percentage of patients achieving MMR [4]. However when patients were analyzed in terms of the dose of imatinib they actually received, the CCyR was 91% for patients receiving 700–800 mg of imatinib, 73% for patients receiving 400–699 mg and only 20% for patients receiving less than 400 mg of imatinib. Whether the faster achievement of MMR will translate into improved long term outcome remains to be determined. When time to response was measured on the German CML Study IV, achievement of MMR by 18 months was a strong predictor of event free survival [5]. Similarly, in a retrospective study from Australia, the early achievement of molecular response was predictive of event free survival [6]. Events occurred in 0/41 patients achieving MMR by 6 months, 3/40 (8%) of patients achieving MMR in 6–12 months, and 5/22 (15%) of patients achieving MMR by 12–18 months.

Prior to imatinib, interferon and ara-C were the mainstays of therapy. The SPIRIT Trial is studying whether the addition of ara-C or pegylated interferon to imatinib will result in an increased percentage of patients with MMR [7]. Although many patients were unable to tolerate the increased toxicity of the combination therapy, the percentage of patients with MMR was 57% for patients randomized to imatinib plus pegylated interferon versus 38% for patients randomized to imatinib 400 mg as a single agent, p = 0.0008. Again, whether this translates into improved long term outcome remains to be determined.

Many patients who progress on imatinib respond to second line therapy with either nilotinib or dasatinib. Nilotinib is an imatinib analogue with more specific BCR/ABL binding. Dasatinib is a dual SRC/ABL kinase inhibitor. Both are effective against a large number of BCR/ABL kinase mutations with the exception of the T315I mutation. Newer studies are evaluating the efficacy of these agents in the front line setting [8,9]. Both agents lead to high rates of CCyR at 12 months (nilotinib: 93%, dasatinib: 95%, imatinib historical control: 65%, respectively), and MMR at 18 months (nilotinib: 65%, dasatinib: 48%, respectively). Dasatinib toxicity includes pleural effusions in 20% of patients and hemorrhage even in the absence of thrombocytopenia. A change in the dose and schedule of dasatinib to 100 mg orally daily has resulted in a decrease in these toxicities with the maintenance of efficacy. Patients receiving nilotinib require monitoring of QTc, potassium and magnesium to prevent arrhythmias. Further follow up is needed before these agents will be considered standard frontline therapy.

An important question is whether patients with CML can be cured with imatinib. Early reports of pregnant women discontinuing imatinib noted a very high rate of relapse. A more formal study allowed patients who had been in CMR for at least 2 years to stop imatinib [10]. Although half of the patients relapsed rapidly, many of the patients remain in CMR without further therapy. Interestingly, there was trend towards a lower relapse rate in patients who had exposure to interferon prior to imatinib. Most of the patients who relapsed were sensitive to retreatment to imatinib. However it is too early to recommend the discontinuation of imatinib outside of a clinical trial.

A number of new agents are currently under study. Bosutinib is a dual ABL/SRC kinase inhibitor that has minimal inhibition of PDGFR and c-kit. This agent leads to high rates of major cytogenetic and MMR in patients with CML-CP who are imatinib intolerant (51% and 39%, respectively) or resistant (45% and 42%, respectively) [11]. Bosutinib also yields major cytogenetic remissions and MMR in patients who have resistant to both imatinib and dasatinib. Toxicity includes myelosuppression as well as elevations in amylase and lipase. Patients with T315I mutations remain a treatment challenge. Options include aurora kinase inhibitors and allogeneic stem cell transplantation. Omacetaxine mepesuccinate (homoharringtonine) is also being studied [12]. In the past the development of this agent was limited by toxicity, including myelosuppression and the need for prolonged intravenous administration to avoid hypotension. Recently a subcutaneous formulation has been studied in patients with T315I mutations. Complete hematologic remission was seen in 80% of patients in chronic phase and 18% of patients with accelerated phase CML. Toxicity included myelosuppression and febrile neutropenia.

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