Next Generation Therapy in Chronic Myeloid Leukemia

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TKIs Imatinib is an established first-line therapy CP of CML. Before Imatinib therapy, IFN- α was a treatment option for CML because it induced durable remissions in a subset of CP patients. However, because of IFN toxicity, and its limited and unpredictable efficacy, IFN- α was displaced by Imatinib, with its limited toxicity and marked efficacy in the treatment of most CML patients. Imatinib has limitations, but the 5-year survival rate with Imatinib is approx. 89% compared with Interferon and Cytarabin (70%). About 15–20% CML become resistant to Imatinib, and the resistance is found in association with a BCR/ABL mutation T315I or with G250E mutations. Treatment of Imatinib-resistance CML is thus a challenge in clinical hematology. In addition, clinical evaluation of Imatinib has shown adverse effects, such as fatigue, severe nausea,

vomiting, oedema, fluid retention, muscle cramps, muscular skeletal pain, and cutaneous disorders. With the prolonged survival time in CML, which with Imatinib is a median 40 months, BCC, SCC, melanoma (30% cases), breast cancer (the authors have found 1 case), prostate cancer (1 case), GI cancer, GU bladder cancer including RCC, a few pancreatic and cholangiocarcinomas, and metastatic carcinoma of unknown origin have also been reported in various literature [1]. These investigators concluded that increased rates of cancers were found at a large range of sites and there was immune deficiency, regardless of the mechanism of deficiency. There have also been scattered reports of co-existence of CML with other lymphoid malignancies such as CLL and multiple myeloma [1, 2]. It has also been shown that heart failure occurs in 1 in 1,000 patients receiving Imatinib, and that it also alters bone metabolism. Imatinib costs more than the Interferon + Cytarabin combination. The effects of Imatinib (as well as other kinase inhibitors) on leukemic stem or initiating cells are limited, and so it has been advisable to take a low dose of Imatinib over a long period.

Now, the second generation TKIs, such as Dasatinib and Nilotinib, have appeared. A unique spectrum of adverse events has occurred and been reported for both these TKIs [3, 4]. For Dasatinib-treated patients, the occurrence of pleural effusion has been a clinical challenge, especially when pleural effusion becomes recurrent or is accompanied by pericardial effusion, pulmonary hypertension, or an infection. Also, potential risk factors such as a pre-existing cardiac disease, arterial hypertension, or auto-immune disorders have been described for these TKIs. Several non-hematologic adverse events have been described for Dasatinib, including diarrhea, skin rash, bleeding, viral re-activation, and sometimes also many opportunistic infections, which have been reported in patients receiving

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Dasatinib at a dose of 270 mg daily. Nilotinib-treated patients have developed increases in pancreatic enzymes, bilirubin, and fasting glucose levels. Other non-hematologic adverse events of Nilotinib include diarrhea, folliculitis-like skin rash, and bleeding. There are a few reports of severe peripheral arterial occlusive disease (PAOD) and other vascular occlusive events (infarction) in patients receiving Nilotinib [3, 4]. Several of these patients developed a rapidly progressive and highly resistant form of PAOD after switching from Imatinib to Nilotinib [3, 4]. The question is whether patients, who had a complete molecular response (CMR or MCyR) to Imatinib or Imatinib in combination with Interferon, could safely stop drug treatment? What should be done with relapses? Do TKIs act then? SCT is still the treatment for CML that is considered to be curative in patients with AP or blast-crisis CML. Other choices which are still in clinical trial include a vaccine called CMLVAX100 which is given along with Imatinib to see if there is an increase in its effectiveness. Research into this and other cancer vaccines is continuing. The oral agent AP24534 also appears to have some activity independent of Bcr-Abl mutation. Cortes and colleagues [5] conducted a trial of AP24534 in patients with refractory CML and other hematologic malignancies. This agent

inhibits survival of cell lines expressing Bcr-Abl variants at an inhibitory concentration of less than 40 nM. It also inhibits Flt-3 and c-Src. And this agent has the advantage of being orally administered.

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