INTERVIEW

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Tracks 1-13

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Track 2 Selection of front-line treatment for Philadelphia chromosome-positive CP-CML

Track 3 Response to second-generation tyrosine kinase inhibitors (TKIs) in patients with imatinib-intolerant CML

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Track 8 **Case discussion:** A 48-year-old man with CML with a BCR-ABL G250E mutation has a complete cytogenetic response but experiences relapse after two years of imatinib

Track 9 **Case discussion:** A 61-year-old woman with multiple TKI-refractory CP-CML and a T315I mutation receives the pan-BCR-ABL inhibitor ponatinib

Track 10 Third-generation oral pan-BCR-ABL TKI ponatinib under development in CML

Track 11 **Case discussion:** A 68-year-old woman with myelodysplastic syndrome (MDS) and a diploid karyotype, pancytopenia and 16 percent bone marrow blasts is treated with decitabine

Track 12 Potential advantages of orally administered azacitidine for patients with MDS

Track 13 Lenalidomide in the treatment of MDS with the 5q- abnormality

Select Excerpts from the Interview

Tracks 2-3

DR LOVE: What is your approach to selection of first-line therapy for a patient with chronic-phase chronic myelogenous leukemia (CML)?

DR JABBOUR: Three options have been approved by the FDA — imatinib, nilotinib and dasatinib. The question is, which therapy do you start with? One question I receive from community oncologists is, "Can I start patients on imatinib and switch to one of the newer agents if the patient is not responding

well?" My answer is, "You may never have a second chance. You go to the war with the best weapons you have."

At eight years of follow-up with imatinib, 35 percent of patients either responded and lost their response or never responded (Deininger 2009). If you administer second-line salvage therapy with either nilotinib or dasatinib, only 50 percent of patients will respond, so why wait until the second line to go to these agents?

Nilotinib and dasatinib both have shown increased rates of complete cytogenetic response (CCyR) by 12 months (Saglio 2010; Kantarjian 2010). Why is that important? If you can improve the rate of CCyR by 12 months, then you can improve survival. That correlation needs to be shown in the future, but at least we have a surrogate endpoint. Major molecular response — another secondary endpoint — is also improved with these agents compared to imatinib.

Nilotinib has also been reported to improve transformation-free survival significantly (Saglio 2010). Patients with CML die only if their disease transforms, so if nilotinib can reduce the rate of transformation, patients can survive with chronic-phase CML for a long time. We are no longer administering imatinib in a front-line setting based on this evidence.

How to best select among the second-generation agents is a hard decision as we administer both of these agents. The DASISION trial did not show the rate of improvement in transformation with dasatinib that was reported with nilotinib in the ENESTnd trial. However, nilotinib is administered twice daily and dasatinib once a day, so one aspect to consider is the patient's rhythm of life. If a patient is traveling all the time, for example, I tend to opt for dasatinib.

Comorbidities should also be considered. If I have a patient who is a smoker and who has hypertension, I avoid dasatinib because of the risk of pleural effusion.

DR LOVE: How often do you have patients referred to you with intolerance to imatinib, and if you're going to switch to one of the other available agents, how do you make that decision at that point?

DR JABBOUR: We're seeing more patients with intolerance. In the past, switching was rare because we had no other options. In my experience, if a patient was responding to imatinib and then becomes intolerant, a switch to either nilotinib or dasatinib will be effective. If the patient has not experienced a response to imatinib, the likelihood of experiencing a response to a second-generation tyrosine kinase inhibitor is not as great.

Generally, if I have a patient who has a major problem with intolerance to imatinib, it's occurring as a result of pancytopenia. In this case, I would prefer switching to nilotinib.

Given a patient with an imatinib-related skin rash, I may opt for dasatinib because skin rash has been observed with nilotinib. Overall, cross intolerances between imatinib and nilotinib or imatinib and dasatinib are extremely rare.

Track 12

DR LOVE: Can you discuss the recent *Journal of Clinical Oncology* publication from your group on orally administered azacitidine in myelodysplastic syndromes (MDS)?

DR JABBOUR: Oral azacitidine is promising, and we're administering it up front for patients with MDS (Garcia-Manero 2011; [3.1]).

We have observed increased platelet counts in these patients, which could be a result of the azacitidine therapy. So high platelets at the beginning of therapy should not be a discouraging sign. It could be an effect caused by the therapy because after approximately a month of treatment, the platelet count decreases and a response begins to appear. ■

3.1

Phase I Study of Oral Azacitidine* for Patients with Myelodysplastic Syndromes, Chronic Myelomonocytic Leukemia or Acute Myeloid Leukemia†

Response	First line (n = 15)	Previously treated (n = 17)
Overall response (excluding mCR)	73%	35%
Complete remission‡	40%	0%
Hematologic improvement	56%	38%
Erythroid	50%	30%
Neutrophil	29%	0%
Platelet	33%	36%
Bone marrow complete remission (mCR)	33%	67%

* One cycle of subcutaneous azacitidine (75 mg/m^2) on the first seven days of cycle one followed by oral azacitidine daily (120 to 600 mg) on the first seven days of each additional 28-day cycle
† No patients with acute myeloid leukemia experienced a response
‡ Patients achieving complete remission were not included in any other categories

Garcia-Manero G et al. *J Clin Oncol* 2011;29(18):2521-7.

SELECT PUBLICATIONS

Deininger M et al. **International Randomized Study of Interferon vs STI571 (IRIS) 8-year follow up: Sustained survival and low risk for progression or events in patients with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) treated with imatinib.** *Proc ASH* 2009;**Abstract 1126**.

Garcia-Manero G et al. **Phase I study of oral azacitidine in myelodysplastic syndromes, chronic myelomonocytic leukemia, and acute myeloid leukemia.** *J Clin Oncol* 2011;29(18):2521-7.

Kantarjian H et al. **Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia.** *N Engl J Med* 2010;362(24):2260-70.

Saglio G et al. **Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia.** *N Engl J Med* 2010;362(24):2251-9.