INTERVIEW

Jorge E Cortes, MD

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Tracks 1-11

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Tracks 1, 5-6

DR LOVE: Would you discuss what we know about the various approved tyrosine kinase inhibitors (TKIs) in chronic myeloid leukemia (CML)?

DR CORTES: The long-term follow-up data of the ENESTnd trial of nilotinib (Saglio 2013) and the DASISION trial of dasatinib (Cortes 2013a) were presented at ASH 2013. The results are reassuring because they continue to be positive, with durable long-term responses and the incidence of deeper molecular responses continuing to be greater for patients who receive dasatinib or nilotinib compared to imatinib.

Longer follow-up data with imatinib also indicate that patients fare well (Kantarjian 2012). Although many no longer experience a response to imatinib, approximately 60% of those who started imatinib therapy about 10 to 15 years ago are still faring well.

Also, data show that higher doses of imatinib are effective in CML. Although this increases toxicity, in the long term the results are better. These results are important because generic imatinib will soon become available. However, for optimal results, I would treat CML with a second-generation TKI.

DR LOVE: Could you describe the study by your group presented at ASH 2013 evaluating the incidence of acute and chronic renal failure among patients with CML treated with TKIs?

DR CORTES: Any of the TKIs bring the potential for renal dysfunction. Long-term imatinib therapy may result in a decline in glomerular filtration rates (Yilmaz 2013; [4.1]). This seems to be more prominent with imatinib than with dasatinib or nilotinib. It is an event that we need to monitor carefully and one that needs to be addressed promptly. It will occur more frequently in elderly patients and those with risk factors such as diabetes and hypertension.

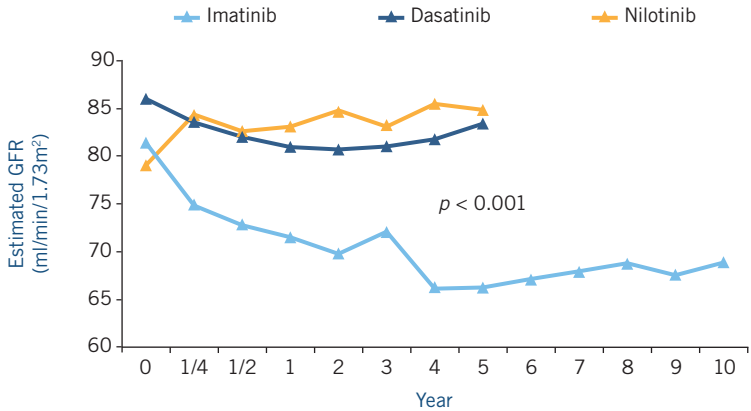
DR LOVE: Can you comment on patient compliance when undergoing TKI therapy?

DR CORTES: Some studies have addressed the time needed for TKI interruption for a patient to experience relapse. Patient adherence during the first 3 months was studied to assess how this affects the probability of achieving the best molecular response at 3 months (Apperley 2013). Patients who experienced any treatment interruption, even as short as 1 day, have a reduced probability of achieving a good response at 3 months. If it's more than 14 days, the chance of achieving the deeper molecular response is much lower.

Careful monitoring every 3 to 6 months allows you to discuss with the patient the importance of the long-term treatment goals. Also, it provides the opportunity to keep emphasizing what the results mean and what the potential implications of missing a dose could be. I discuss it every 3 to 6 months with all my patients.

4.1

Changes in Glomerular Filtration Rates (GFR) in Patients with Chronic Myeloid Leukemia Treated with Tyrosine Kinase Inhibitors (TKIs)



Conclusion: Long-term treatment with imatinib may cause a significant decline in estimated GFR. Interestingly, treatment with nilotinib may cause a slight improvement in GFR. It is important that patients are monitored for renal function during therapy with TKIs, with particular attention to those with risk factors for renal dysfunction.

With permission from Yilmaz et al. *Proc ASH* 2013;**Abstract 1488**.

Tracks 10-11

DR LOVE: What is your clinical experience with the second-generation TKI bosutinib?

DR CORTES: I use it frequently. Bosutinib works well after imatinib failure, achieving a similar response rate to dasatinib or nilotinib. It has activity in the third-line setting, with about 30% to 40% of patients achieving a major cytogenetic response. It's fairly safe and causes low cardiac toxicity. It is associated with gastrointestinal toxicity — diarrhea, in particular — which tends to be transient and manageable.

DR LOVE: What is the current status of ponatinib in CML, and how do you envision it being used in the future?

DR CORTES: Ponatinib is an outstanding agent from an efficacy viewpoint. Patients for whom 2 or more TKIs have failed or those with the T315I mutation achieve high response rates on ponatinib. None of the other TKIs is as potent.

The marketing and sales of ponatinib were temporarily suspended recently because of the risk of serious thrombosis and stenosis. However, ponatinib is back on the market but with more warnings to make physicians aware of these risks and so that patients are properly selected and carefully monitored to reduce these risks. Studies of front-line ponatinib were going on when its marketing was temporarily suspended. The results from a single-arm front-line study at our institution were outstanding (Cortes 2013b). I believe it can be used in many other settings. We need more studies, particularly exploring ways to reduce its toxicity.

Track 9

DR LOVE: Would you discuss the role of omacetaxine as a single agent or in combination therapy with a TKI for CML?

DR CORTES: Omacetaxine is a valuable agent, but its schedule of administration is unfriendly because it's administered subcutaneously twice a day. It has to be administered in the doctor's office. Future studies will investigate fixed doses and once-daily schedules. The combination of omacetaxine with a TKI will be attractive in blast-phase CML because the TKI alone is not good enough. We are about to start a study in which patients with minimal residual disease on a TKI will receive a small dose of omacetaxine in addition to the TKI. Although omacetaxine appears to be effective at eradicating leukemic stem cells in vitro, the TKIs are unable to do so. ■

SELECT PUBLICATIONS

Apperley JF et al. **Dose interruption/reduction of tyrosine kinase inhibitors in the first 3 months of treatment of CML is associated with inferior early molecular responses and predicts for an increased likelihood of discontinuation of the 1st line agent.** *Proc ASH* 2013;**Abstract 93**.

Cortes JE et al. **Four-year (yr) follow-up of patients (pts) with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) receiving dasatinib or imatinib: Efficacy based on early response.** *Proc ASH* 2013a;**Abstract 653**.

Cortes JE et al. **Ponatinib as initial therapy for patients with chronic myeloid leukemia in chronic phase (CML-CP).** *Proc ASH* 2013b;**Abstract 1483**.

Kantarjian H et al. **Very long-term follow-up results of imatinib mesylate therapy in chronic phase chronic myeloid leukemia after failure of interferon alpha therapy.** *Cancer* 2012;118(12):3116-22.

Saglio G et al. **ENESTnd update: Nilotinib (NIL) vs imatinib (IM) in patients (pts) with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) and the impact of early molecular response (EMR) and Sokal risk at diagnosis on long-term outcomes.** *Proc ASH* 2013;**Abstract 92**.

Yilmaz M et al. **Estimated glomerular filtration rate changes in patients (pts) with chronic myeloid leukemia (CML) treated with tyrosine kinase inhibitors (TKI).** *Proc ASH* 2013;**Abstract 1488**.