INTERVIEW

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Tracks 1-12

Select Excerpts from the Interview

Tracks 1-3

DR LOVE: What is your approach to the choice of tyrosine kinase inhibitor (TKI) for first-line therapy in chronic myeloid leukemia (CML)?

DR JABBOUR: Imatinib, nilotinib and dasatinib are available for front-line therapy. For patients with low-risk disease, I would recommend imatinib because the advantage of the second-generation TKIs dasatinib or nilotinib is marginal and yields no effect on survival. I start with imatinib and switch therapy at 3 to 6 months if the response is not good.

For patients who are young and have high-risk features, I would consider dasatinib or nilotinib up front. My choice would be based on comorbidities. I would avoid dasatinib for patients who are at risk for pleural effusion and offer them nilotinib instead. In contrast, for patients with diabetes or cardiovascular issues, I would opt for dasatinib.

In the future, the cost of these agents will also dictate our choice of therapy, especially when generic imatinib becomes available.

DR LOVE: Ponatinib is a potent TKI used for patients who are resistant/intolerant to dasatinib or nilotinib or those with the T315I mutation. What is known about the cardiovascular side effects with ponatinib?

DR JABBOUR: Ponatinib is associated with a higher incidence of cardiovascular events compared to other TKIs. Arterial events are observed at a rate of approximately 13% per year of therapy. This does not increase with time on therapy. Both venous and arterial events are observed. When these events occur, the drug must be discontinued.

Based on the PACE trial, patients with certain risk factors at baseline, such as cardiac disease, diabetes or advanced age, are at higher risk of developing vascular events (Cortes 2013). We try to optimize risk factors before starting patients on ponatinib. Because the agent is potent and you can minimize side effects by reducing the dose, in our practice we administer 30 mg per day and reduce to 15 mg.

DR LOVE: What are your thoughts on the role of omacetaxine, another drug approved for CML?

DR JABBOUR: Omacetaxine inhibits protein translation and has shown activity in patients who are resistant or intolerant to multiple TKIs and those with the T315I mutation. In a pivotal trial that led to the approval in chronic phase, 23% of patients achieved a major cytogenetic response (Cortes 2012). For patients in blast phase, the combination of omacetaxine and a TKI is attractive. It can be considered off label with a TKI in patients for whom you want to stop therapy.

As induction therapy, the drug is administered subcutaneously twice daily for 2 weeks. It can now be administered at home, which is more practical for patients. In my practice, I administer it for 1 week at the start and then for 3 days later to minimize the risk of myelosuppression.

Tracks 5-7

DR LOVE: What is your clinical experience with ruxolitinib for polycythemia vera (PV)?

DR JABBOUR: The main goal is to achieve hematocrit control and improve symptoms in patients with PV. The response to ruxolitinib in PV is rapid because myelosuppression is not as much of a concern as it is with myelofibrosis (MF). I have found it to be a well-tolerated agent. The blood counts must be closely monitored early on and the dose adjusted if necessary. Patients usually receive 10 mg BID and experience a dramatic improvement in quality of life. In the RESPONSE trial, assessing ruxolitinib versus best available therapy in patients with PV who had an inadequate response to or unacceptable side effects from hydroxyurea, the probability that a response to ruxolitinib would be maintained for 1 year was approximately 90% (Vannucchi 2015; [3.1]).

DR LOVE: How do you approach dosing of ruxolitinib in patients with anemia and thrombocytopenia?

DR JABBOUR: For patients who have platelet counts on the order of 100 or 110 x 10^9/L, I usually start with a 10-mg dose and titrate upward. A dose of 10 mg BID or higher is necessary to have an effect on the spleen. I will monitor blood counts on a

3.1

RESPONSE: Efficacy Results of a Phase III Trial of Ruxolitinib (RUX) versus Best Available Therapy (BAT) for Polycythemia Vera (PV)

Response	RUX (n = 110)	BAT (n = 112)	*p*-value
Composite primary endpoint	20.9%	0.9%	<0.001
≥35% reduction in spleen volume	38.2%	0.9%	—
Hematocrit control	60.0%	19.6%	—

- Composite primary endpoint: Hematocrit control and >35% reduction in spleen volume at week 32
- Significantly more patients in the RUX group than in the BAT group had a complete hematologic response: 23.6% vs 8.9%, $p = 0.003$
- Treatment with RUX was associated with greater and clinically meaningful improvements in PV-related symptom burden and quality-of-life measures compared to standard therapy
- The probability that a primary response to ruxolitinib would be maintained for 1 year from the time of the initial response was 94%

Vannucchi A et al. *N Engl J Med* 2015;372(5):426-35; Mesa R. et al. *Proc ASH* 2014;**Abstract 709**.

weekly basis and escalate every 4 weeks to reach 20 mg BID or higher. The goal is to avoid discontinuing therapy. If therapy is stopped, the benefits are lost within 7 days and patients start experiencing symptoms again. Drugs like danazol can be used in combination with ruxolitinib to manage the anemia.

DR LOVE: What do we know about the novel agent pacritinib in the treatment of myeloproliferative neoplasms?

DR JABBOUR: Pacritinib is a JAK2 inhibitor that has similar efficacy to ruxolitinib. The main advantage of pacritinib versus ruxolitinib is that it doesn't cause as much myelosuppression. If pacritinib were available, I would consider it for patients who have baseline anemia or thrombocytopenia. The main side effects are gastrointestinal toxicities like diarrhea, nausea and vomiting, which can be managed with dose reductions. The drug is promising and is also being evaluated in patients with low counts compared to best available therapy, including ruxolitinib.

DR LOVE: What other novel agents are being investigated in MF?

DR JABBOUR: A number of new agents are being evaluated. They include histone deacetylase inhibitors and antifibrotic agents. With histone deacetylase inhibitors, more side effects are encountered. A promising therapy for patients who have the mixed syndrome of myelodysplastic syndrome/myeloproliferative neoplasm is the combination of azacitidine and ruxolitinib, which can be considered sequentially instead of concurrently to improve outcomes and reduce the risk of side effects.

Track 10

DR LOVE: Would you discuss the results of the SORAML trial of sorafenib in addition to standard therapy for younger patients with newly diagnosed acute myeloid leukemia (AML)?

DR JABBOUR: In the SORAML study, an advantage was observed overall with sorafenib versus placebo among patients with AML in the front-line setting, independent of FLT3-ITD status (Rollig 2014; [3.2]). It cannot be determined from the study

3.2

SORAML: Results of a Phase II Trial of Sorafenib versus Placebo with Standard Therapy for Younger Patients with Newly Diagnosed Acute Myeloid Leukemia (AML)

Outcome	Sorafenib	Placebo	*p*-value
Complete response (CR)	60%	59%	0.764
Median event-free survival (EFS)* 3-year EFS rate	20.5 mo 40%	9.2 mo 22%	0.013
Median relapse-free survival (RFS) 3-year RFS rate	NYR 56%	23 mo 38%	0.017
Median overall survival (OS) 3-year OS rate	NYR 63%	NYR 56%	0.382

NYR = not yet reached

* An event is defined as failure to achieve CR after induction, relapse or death.

- The most common reported Grade ≥3 adverse events were fever (40%), infections (22%) and bleeding events (2%).
- The risk of fever, bleeding events and hand-foot syndrome was significantly higher on the sorafenib arm.
- The incidence of all other adverse events showed no significant difference between arms.

Rollig C et al. *Proc ASH* 2014;Abstract 6.

if sorafenib increases overall survival. Although sorafenib has not been approved in this setting, it can be considered in combination with chemotherapy for patients with AML who have the FLT3-ITD mutation.

Track 11

DR LOVE: What are your thoughts on the use of the novel Bcl-2 inhibitor venetoclax (ABT-199), an agent for which breakthrough therapy designation was recently granted by the FDA for patients with CLL and deletion 17p, for patients with AML?

DR JABBOUR: Venetoclax is one of the most promising agents under investigation for patients with AML. A study presented at ASH 2014 demonstrated encouraging activity with this agent in patients with heavily treated AML (Konopleva 2014). Ongoing trials are evaluating the combination of venetoclax with decitabine or azacitidine.

I have 3 patients with AML who were unfit for chemotherapy to whom I administered venetoclax in combination with decitabine. They achieved a remission after 1 course, which is unheard of. One major toxicity with this therapy is neutropenia. Tumor lysis syndrome is a concern, but it is not a major problem. I employ dose escalation with venetoclax and monitor patients carefully. ■

SELECT PUBLICATIONS

Cortes JE et al. **A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias.** *N Engl J Med* 2013;369(19):1783-96.

Cortes JE et al. **Phase 2 study of subcutaneous omacetaxine mepesuccinate after TKI failure in patients with chronic-phase CML with T315I mutation.** *Blood* 2012;120(13):2573-80.

Konopleva M et al. **A Phase 2 study of ABT-199 (GDC-0199) in patients with acute myelogenous leukemia (AML).** *Proc ASH* 2014;**Abstract 118**.