INTERVIEW

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Tracks 1-2

DR LOVE: Would you discuss some of the most promising new agents and strategies under investigation for patients with acute myeloid leukemia (AML)?

DR STEENSMA: One area of interest involves investigation of agents targeting FLT3 mutations, which are driver mutations commonly associated with AML. The 2 general classes of FLT3 mutations are internal tandem duplication (ITD) mutations and tyrosine kinase domain (TKD) mutations. Both constitutively activate the FLT3 receptor, but ITD mutations tend to be associated with more proliferative disease and a poorer prognosis, and they're more common than TKD mutations. Some kinase inhibitors will inhibit both ITD and TKD, and some will inhibit only ITD.

FLT3 inhibitors have typically shown relatively limited efficacy as single agents. They're often used in the salvage setting after the disease has relapsed. Sorafenib has FLT3-ITD inhibitory activity and has been used in relapsed/refractory FLT3-positive AML, resulting in remission in some patients. Data presented during the plenary session at ASH 2014 from a study in which sorafenib was added to "7 plus 3" chemotherapy indicated that patients receiving that combination fared better in terms of relapse-free survival. A trend toward improved OS regardless of FLT3 status was also apparent (Rollig 2014).

One novel FLT3 inhibitor that is active as a single agent in AML is gilteritinib (ASP2215). Single-agent gilteritinib has demonstrated a high complete response rate (Levis 2015; [2.1]). When you inhibit the FLT3 receptor, the cells upregulate the ligand to try to circumvent the inhibition, and that's been a challenge that some other FLT3 inhibitors have faced in the past that's delayed their development.

Another interesting agent in this drug class that is being evaluated in combination with 7 plus 3 is midostaurin. Exciting data from the Phase III CALGB-10603 (RATIFY) trial were presented at ASH 2015 (Stone 2015; [2.2]). These FLT3 inhibitors primarily differ with respect to the narrowness of their kinase inhibitory profiles.

2.1

Results of a Phase I/II Dose-Escalation Study of the Potent FLT3/AXL Inhibitor Gilteritinib (ASP2215) for Patients with Relapsed/Refractory Acute Myeloid Leukemia

	Clinical response by mutation status		
	FLT3 mutation-positive		FLT3 wild type
	20-450 mg (n = 127)	**≥80 mg** (n = 106)	**20-450 mg** (n = 57)
ORR (CRc + PR)	52%	57.5%	8.8%
CRc (CR + CRp + CRi)	40.9%	47.2%	5.3%
CR	6.3%	6.6%	0%
CRp	3.9%	4.7%	1.8%
CRi	30.7%	35.8%	3.5%
PR	11.0%	10.4%	3.5%

ORR = overall response rate; CR = complete remission; CRc = composite CR; PR = partial remission; CRp = CR with incomplete platelet recovery; CRi = CR with incomplete hematologic recovery

- Treatment-related adverse events included diarrhea (13.4%), fatigue (12.4%), anemia (7.2%), peripheral edema (7.2%), nausea (6.7%) and dysgeusia (5.2%).
- Serious adverse events included febrile neutropenia (27.3%), sepsis (11.9%), pneumonia (8.8%), hypotension (5.7%) and respiratory failure (5.7%).

Levis MJ et al. *Proc ASCO* 2015;**Abstract 7003**.

Tracks 8-9

CASE DISCUSSION: A 65-year-old woman with hydroxyurea-resistant polycythemia vera receives ruxolitinib

DR STEENSMA: Most patients with polycythemia vera fare well with only phlebotomy and aspirin or, if they are considered to be at higher risk, meaning they are older than age 60 or have experienced a prior thrombosis, then phlebotomy in combination with aspirin and hydroxyurea. Some patients don't fare so well, however, and this 65-year-old woman was one of them. She had received hydroxyurea after presenting with polycythemia vera, and one symptom that the hydroxyurea was unable to control was severe bone pain, especially in her ribs and spine. She also developed constitutional symptoms, such as night sweats, that weren't as severe.

We discussed other options, including pegylated interferon or ruxolitinib, to control her pain. She opted to try ruxolitinib, which was recently approved by the FDA for patients who are intolerant to or have inadequate response to hydroxyurea. Her bone pain did not completely go away but got much better, and ruxolitinib also improved

2.2

Phase III CALGB-10603 (RATIFY) Trial of Midostaurin in Combination with Daunorubicin/Cytarabine Induction and High-Dose Cytarabine Consolidation and as Maintenance Therapy for Patients with Newly Diagnosed Acute Myeloid Leukemia with FLT3 Mutations

Efficacy	Midostaurin (n = 360)	Placebo (n = 357)	Hazard ratio	*p*-value
Median OS	74.7 mo	26.0 mo	0.77	0.007
Median OS, SCT censored*	NR	NR	0.77	0.047
Median EFS	8.0 mo	3.0 mo	0.80	0.0044
Median EFS, SCT censored*	8.2 mo	3.0 mo	0.84	0.025

OS = overall survival; SCT = stem cell transplant; NR = not reached; EFS = event-free survival

* Censored for transplant analyses

No statistically significant differences were observed in the overall rate of Grade ≥3 hematologic or nonhematologic adverse events between midostaurin and placebo.

Stone RM et al. *Proc ASH* 2015;**Abstract 6**.

her associated symptoms. So I believe a small niche exists in polycythemia vera for JAK inhibitors, but by no means should they be the first-line therapy because hydroxyurea is inexpensive and we have many years of experience with it.

DR LOVE: What is your clinical experience with patients in whom ruxolitinib needs to be discontinued?

DR STEENSMA: One of the most common questions I hear from community oncologists is whether ruxolitinib can be discontinued for patients who are not faring well. I was involved in the early trials of ruxolitinib, and when patients were hospitalized for an infection, for example, and ruxolitinib was stopped suddenly, their condition became much worse. They experienced something of a "cytokine storm," and a couple of patients had to be intubated or even died.

An infection or major operation will trigger cytokine release, so a patient who is acutely ill with an infection is not someone for whom you want to suddenly stop a JAK inhibitor, because JAK inhibitors block cytokine signaling. Ruxolitinib is a highly potent inhibitor of cytokines involved in infection and inflammation. That's probably why patients feel much better and why their symptoms improve after starting therapy with ruxolitinib.

If you suddenly stop the JAK inhibitor, you reverse the benefit received from treatment and patients can become seriously ill. So JAK inhibitors should not be stopped abruptly in those situations. But it is acceptable to stop ruxolitinib "cold turkey" in certain cases — for example, for patients who are chronically ill and have been receiving ruxolitinib for 3 to 4 months without any benefit. ■

SELECT PUBLICATIONS

Levis MJ et al. **Results of a first-in-human, phase I/II trial of ASP2215, a selective, potent inhibitor of FLT3/Axl in patients with relapsed or refractory (R/R) acute myeloid leukemia (AML).** *Proc ASCO* 2015;**Abstract 7003**.

Rollig C et al. **Sorafenib versus placebo in addition to standard therapy in younger patients with newly diagnosed acute myeloid leukemia: Results from 267 patients treated in the randomized placebo-controlled SAL-SORAML trial.** *Proc ASH* 2014;**Abstract 6**.