INTERVIEW

Harry P Erba, MD, PhD

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Tracks 1-13

Select Excerpts from the Interview

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DR LOVE: Are there any promising new agents or strategies in the treatment of acute myeloid leukemia (AML), particularly in terms of treatment for older patients?

DR ERBA: One strategy that I am excited by now in my role as chair of the SWOG Leukemia Committee is an Intergroup collaboration of translational and clinical scientists that we've convened to develop the next clinical trial for older patients with AML. ECOG is currently investigating "3 + 7" versus clofarabine and also asking a decitabine maintenance question. That study will end soon, and we're designing the next trial.

DR LOVE: Omacetaxine, which is an agent approved by the FDA for patients with chronic myeloid leukemia, also has reported activity in combination with low-dose

cytarabine for older patients with AML who are not fit enough for intensive chemotherapy (Kadia 2013). Have you administered this agent in the AML setting?

DR ERBA: Omacetaxine does have activity in AML, but I have not used it yet. However, it is one of the agents that we are considering for a randomized Phase II study for older patients with AML. Another promising agent is the polo-like kinase inhibitor volasertib.

Volasertib has been studied in a Phase II trial of low-dose cytarabine with or without volasertib for older patients with AML who were not believed to be candidates for intensive induction chemotherapy. Event-free survival was better in the volasertib arm, and a subset of patients with poor-risk cytogenetics experienced a superior response rate with the combination compared to low-dose cytarabine alone (Dohner 2014; [2.1]). Volasertib is now being evaluated in a larger, pivotal Phase III study (POLO-AML-2; NCT01721876), and we anticipate results in the near future.

DR LOVE: Are there any new developments in the management of AML with FLT3 mutations?

DR ERBA: Approximately 25% of patients with AML and a normal karyotype will have an FLT3 mutation, typically an internal tandem duplication (ITD) that's been associated with worse outcomes. Interestingly, FLT3 ITD has not been associated with a lower remission rate, but in adult AML it is associated with lower event-free and overall survival.

A number of agents are in development for AML with FLT3-activating mutations. None has yet been FDA approved for that indication. Sorafenib, which is FDA approved for hepatocellular carcinoma and renal cell carcinoma, also exhibits activity against FLT3 ITD, and Phase II data with sorafenib 400 mg twice daily in combination with azacitidine show biologic activity in patients with relapsed AML and FLT3-ITD mutations (Ravandi 2013).

2.1

Results of a Phase II Trial of Low-Dose Cytarabine (LDAC) with or without Volasertib for Patients with Acute Myeloid Leukemia Not Suitable for Induction Therapy

Efficacy	LDAC (n = 45)	LDAC + volasertib (n = 42)	Hazard ratio/ odds ratio	*p*-value
Median event-free survival	2.3 mo	5.6 mo	0.57	0.021
Median overall survival*	5.2 mo	8.0 mo	0.63	0.047
Overall response rate†	13.3%	31.0%	2.91	0.052
Select adverse events (Grade 3-5)	**LDAC**		**LDAC + volasertib**	
Febrile neutropenia	15.6%		54.8%	
Cellulitis	6.7%		4.8%	
Pneumonia	4.4%		21.4%	
Diarrhea	2.2%		9.5%	
Pyrexia	2.2%		7.1%	

* Estimate of 1-year overall survival rate = 36.8%; 9 (10%) patients were alive and followed for 23.7 to 34.1 months; † Responses in the LDAC/volasertib arm were observed across all genetic groups, including 5 of 14 patients with adverse cytogenetics.

Dohner H et al. *Blood* 2014;124(9):1426-33.

Single-agent quizartinib has demonstrated an approximately 50% response rate for patients with AML and FLT3-ITD mutations (Cortes 2013). A low response rate was also observed for patients with AML that was FLT3 ITD-negative, but the interesting aspect about the definition of *negative* is that the allelic burden would be less than 10%, so you can't rule out the possibility that the marrow simply had a low number of blasts and did express FLT3. In any case, quizartinib elicits responses and is being investigated further in FLT3-positive AML. The FDA is considering it as a single agent.

We are also eagerly awaiting the results of an ongoing CALGB/Alliance study for younger patients with AML and FLT3-ITD mutations. On this study patients are randomly assigned to standard 3 + 7 followed by high-dose cytarabine or the same chemotherapy in combination with the oral FLT3 inhibitor midostaurin during induction, consolidation and as maintenance therapy (CALGB-10603; NCT00651261). I like the design of this study because if you believe a drug will yield a benefit, why not administer it throughout the course of therapy? That's not always done.

Tracks 12-13

DR LOVE: What is your treatment approach for patients with low-risk myelodysplastic syndromes (MDS)?

DR ERBA: We now have more refined molecular analyses to define prognosis, and more information is on the way because we perform whole exome and genome sequencing for patients with MDS. But so far nothing has changed the outlook for these patients. We still have the same discussions about supportive care versus growth factors versus azacitidine or decitabine versus lenalidomide for low-grade or low-risk MDS.

For patients with higher-risk disease, the debate continues with regard to azacitidine or decitabine versus allogeneic stem cell transplantation as the only curative option. These are difficult clinical decisions we must make with our patients, with few randomized data to tell us the best option.

Patients should be considered for stem cell transplantation as soon as possible. Practically speaking, because it takes a while to find a donor and schedule a transplant, I don't see a downside to administering azacitidine or decitabine, especially considering that azacitidine compared to supportive care has been associated with a survival advantage for older patients. I believe that if the patient decides not to go through the transplant, you've done no harm by administering what would otherwise be standard therapy.

We are performing an Intergroup trial of interest in this patient population. We have rapidly enrolled 240 patients on this Phase II study. Patients with high-risk and intermediate-2 risk MDS are randomly assigned to azacitidine alone or azacitidine in combination with either lenalidomide or vorinostat (SWOG-S1117; NCT01522976). ■

SELECT PUBLICATIONS

Cortes JE et al. **Phase I study of quizartinib administered daily to patients with relapsed or refractory acute myeloid leukemia irrespective of FMS-like tyrosine kinase 3-internal tandem duplication status.** *J Clin Oncol* 2013;31(29):3681-7.

Kadia TM et al. **Results of omacetaxine plus low-dose cytarabine (LD-araC) in older patients with acute myeloid leukemia (AML).** *Proc ASCO* 2013;**Abstract 7068**.

Ravandi F et al. **Phase 2 study of azacitidine plus sorafenib in patients with acute myeloid leukemia and FLT-3 internal tandem duplication mutation.** *Blood* 2013;121(23):4655-62.