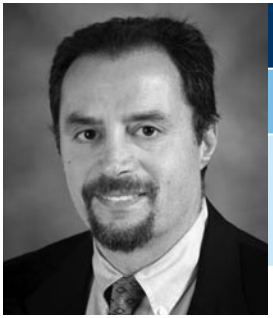

INTERVIEW

Hagop M Kantarjian, MD

Dr Kantarjian is Chairman and Professor in the Leukemia Department at The University of Texas MD Anderson Cancer Center in Houston, Texas.

Tracks 1-17

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Would you comment on the recent advances in the management of MDS?

DR KANTARJIAN: In MDS, the two drugs that are FDA approved and provide benefit to patients are azacitidine and decitabine. Of these two drugs, only azacitidine has shown a survival advantage in a randomized study (Fenaux 2009; [1.1]).

Once patients fail on the hypomethylating agents, the median survival is brief — approximately four to five months. We are studying several agents in this

setting, including clofarabine. A recent publication from our group showed that response rates are in the range of 30 to 40 percent in patients who have failed on azacitidine or decitabine (Faderl 2010).

DR LOVE: What are your thoughts on the alternative dosing schedules of azacitidine and the duration of therapy?

DR KANTARJIAN: We must remember that the survival advantage with azacitidine is with the seven-day regimen. The five-day regimen has been compared to the seven-day regimen, but only the response rates and hematologic improvements were reported and the study did not address survival (Lyons 2009).

If, because of logistical issues, the standard seven-day schedule is not possible during the weekend, my preference is to make up the other two days on the next Monday and Tuesday rather than truncate the schedule to five days because no evidence supports the equivalence of the survival outcome.

Regarding the duration of therapy, I usually offer two years. After two years, I would give the patient the option of either watching and waiting or continuing at the lower-dose schedule or a more infrequent schedule, such as every five to six weeks instead of every four weeks.

1.1

Azacitidine versus Conventional Care Regimens (CCR) for Patients with High-Risk Myelodysplastic Syndromes: Efficacy Data

	Azacitidine (n = 179)	CCR (n = 179)	Hazard ratio	*p*-value
Median overall survival	24.5 months	15 months	0.58	0.0001
Median time to AML	17.8 months	11.5 months	0.50	<0.0001

AML = acute myeloid leukemia

Fenaux P et al. *Lancet Oncol* 2009;10(3):223-32.

Track 3

DR LOVE: What do we know about lenalidomide in MDS or acute myeloid leukemia (AML)?

DR KANTARJIAN: Lenalidomide is an established treatment for patients with del 5q low-risk MDS. The transfusion independence rate of 60 to 70 percent and a complete cytogenetic response rate of approximately 40 percent have been reported in this subset.

The more pertinent issue is to understand the role of lenalidomide in higher-risk MDS or AML. My hope is that clinical trials will also demonstrate a role in higher-risk MDS in combination with azacitidine and, perhaps, for subsets of AML, particularly patients with 5q abnormalities. At this time, it is reasonable to use lenalidomide in combination with growth factors for transfusion-

dependent lower-risk MDS, in which growth factors alone have not worked well and the blasts are still low.

Track 8

DR LOVE: Any new data sets in CLL we should know about?

DR KANTARJIAN: The latest update from the German CLL8 trial shows that FCR improves progression-free survival and overall survival in up-front CLL when compared to FC (Hallek 2009; [1.2]). This has been in the making for many years because the initial pilot studies from MD Anderson reported excellent activity with this regimen in CLL.

1.2

Phase III Study Evaluating Fludarabine, Cyclophosphamide and Rituximab (FCR) versus FC as Initial Therapy for Advanced CLL

	OS at 37.7 months	Median PFS	CR	ORR
FCR	87.2%	51.8 mo	44.1%	95.1%
FC	82.5%	32.8 mo	21.8%	88.4%
p-value	0.012	<0.001	<0.01	<0.01

OS = overall survival; PFS = progression-free survival; CR = complete remission; ORR = overall response rate

Hallek M et al. *Proc ASH* 2009;**Abstract 535**.

Tracks 9, 11

DR LOVE: What about bendamustine in CLL?

DR KANTARJIAN: The studies of bendamustine with rituximab (BR) in the front-line setting are showing a high overall response rate of approximately 90 percent, with a complete response rate in one third of the patients (Fischer 2009; [1.3]). Clearly, this combination is effective in front-line CLL. The question is whether BR is as good as FCR or whether it can rescue patients who have failed on FCR therapy.

DR LOVE: What about bendamustine for elderly patients with CLL or those with comorbidities?

DR KANTARJIAN: I believe this is an important question because, although the FCR data have shown a significant advantage for progression-free survival and for survival, most of the FCR studies enrolled patients younger than age 70 or 75. In fact, at least one German study compared fludarabine to chlorambucil and did not show an advantage with fludarabine in patients older than age 65 (Eichhorst 2009). So, among this subset, BR might have equivalent efficacy to FCR and might be a gentler regimen. We should conduct comparative studies of BR versus FCR among patients with CLL who are older than age 70. In

general, among patients who are older than the age range accrued in the FCR studies, BR is a reasonable approach in the up-front setting.

1.3

Phase II Multicenter Trial of Bendamustine/Rituximab in Advanced Untreated Chronic Lymphocytic Leukemia (N = 117)

OR	CR	PR/nodular PR	SD
90.9%	32.7%	58.2%	9.1%

OR = overall response; CR = complete response; PR = partial response; SD = stable disease

Fischer K et al. *Proc ASH* 2009;**Abstract 205**.

Track 13

DR LOVE: Would you discuss the use of lenalidomide in CLL?

DR KANTARJIAN: Lenalidomide, either as a single agent or in combination with rituximab, has good activity in CLL (Ferrajoli 2009). The responses are slow to occur, so the therapy must be continued. A study from MD Anderson of front-line lenalidomide for elderly patients with CLL was reported at ASCO 2010 (Badoux 2010; [1.4]).

In this study, lenalidomide was started at five mg per day, and approximately 60 patients, all older than age 65, have received treatment so far. The overall response rate is 62 percent with the survival at two years being estimated at 90 percent, which appears to be as good as the FCR regimen.

I believe the lenalidomide/rituximab combination could be interesting, particularly for older patients with CLL because the toxicity of lenalidomide-based regimens can be controlled by starting with a lower dose. Lenalidomide either alone or in combination with rituximab could carve out a possible role in the setting of elderly patients with CLL.

1.4

Phase II Study of Lenalidomide as Initial Treatment of Chronic Lymphocytic Leukemia in Elderly Patients

	NCI Working Group 2008 response (N = 60)	
	Patients, n	%
Complete response (CR)	6	10
CR with incomplete blood cell count recovery	3	5
Partial response (PR)	25	42
Nodular PR	3	5
Overall response rate	37	62

Badoux X et al. *Proc ASCO* 2010;**Abstract 6508**.

Tracks 14, 16

DR LOVE: Would you discuss recent advances in the management of acute promyelocytic leukemia (APL)?

DR KANTARJIAN: Recently, a Phase III Intergroup study was published and showed in a randomized fashion that arsenic trioxide consolidation administered during a short period of two months in the setting of APL provides a survival benefit (Powell 2010; [1.5]). In the clinical setting, I favor the AIDA regimen, which is mostly a combination of ATRA and arsenic trioxide. I believe that of all of the drugs for APL, arsenic trioxide is the most potent. ■

1.5

CALGB-C9710 Phase III Intergroup Study in Acute Promyelocytic Leukemia: Efficacy Outcome (N = 481)

	Standard induction followed by standard consolidation	Standard induction followed by arsenic consolidation and standard consolidation	*p*-value
Three-year EFS	63%	80%	<0.0001
Three-year OS	81%	86%	0.059

EFS = event-free survival; OS = overall survival

Powell BL et al. *Blood* 2010;116(19):3751-7.

SELECT PUBLICATIONS

Badoux X et al. **A phase II study of lenalidomide as initial treatment of elderly patients with chronic lymphocytic leukemia.** *Proc ASCO* 2010;**Abstract 6508**.

Eichhorst BF et al. **First-line therapy with fludarabine compared with chlorambucil does not result in a major benefit for elderly patients with advanced chronic lymphocytic leukemia.** *Blood* 2009;114(16):3382-91.

Faderl S et al. **Oral clofarabine in the treatment of patients with higher-risk myelodysplastic syndrome.** *J Clin Oncol* 2010;28(16):2755-60.

Fenaux P et al. **Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: A randomised, open-label, phase III study.** *Lancet Oncol* 2009;10(3):223-32.

Ferrajoli A et al. **Combination therapy with lenalidomide and rituximab in patients with relapsed chronic lymphocytic leukemia (CLL).** *Proc ASH* 2009;**Abstract 206**.

Fischer K et al. **Bendamustine combined with rituximab (BR) in first-line therapy of advanced CLL: A multicenter Phase II trial of the German CLL Study Group (GCLLSG).** *Proc ASH* 2009;**Abstract 205**.

Hallek M et al. **First-line treatment with fludarabine (F), cyclophosphamide (C), and rituximab (R) (FCR) improves overall survival (OS) in previously untreated patients (pts) with advanced chronic lymphocytic leukemia (CLL): Results of a randomized Phase III trial on behalf of an international group of investigators and the German CLL Study Group.** *Proc ASH* 2009;**Abstract 535**.

Lyons RM et al. **Hematologic response to three alternative dosing schedules of azacitidine in patients with myelodysplastic syndromes.** *J Clin Oncol* 2009;27(11):1850-6.

Powell BL et al. **Arsenic trioxide improves event-free and overall survival for adults with acute promyelocytic leukemia: North American Leukemia Intergroup study C9710.** *Blood* 2010;116(19):3751-7.