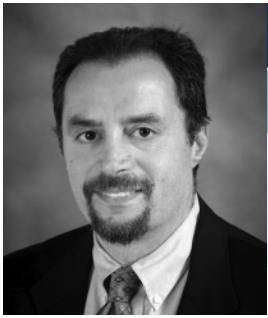

INTERVIEW

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 1-14

Track 1 Novel agents under investigation for FLT3-mutated acute myeloid leukemia (AML)

Track 2 Activity and tolerability of venetoclax alone or in combination with a hypomethylating agent in patients with AML or myelodysplastic syndromes (MDS)

Track 3 Comparison of FLT3 inhibitors midostaurin, quizartinib, gilteritinib and sorafenib in AML

Track 4 Promising investigational agents and strategies in AML

Track 5 Activity of the bispecific T-cell engager blinatumomab in Philadelphia chromosome-negative B-cell precursor acute lymphoblastic leukemia (ALL)

Track 6 INO-VATE: Results of a Phase III trial of the anti-CD22 antibody-drug conjugate inotuzumab ozogamicin versus standard therapy for relapsed/refractory ALL

Track 7 Role of chimeric antigen receptor T-cell therapy in the treatment of relapsed/refractory ALL

Track 8 Monitoring response to TKI therapy for patients with chronic myeloid leukemia (CML) and considerations for discontinuing treatment

Track 9 Choice of first-line TKI therapy for CML and role of generic imatinib

Track 10 Efficacy and long-term outcomes of ruxolitinib in myelofibrosis and polycythemia vera

Track 11 Novel JAK inhibitors under investigation for patients with myeloproliferative neoplasms

Track 12 Activity and ongoing investigation of immune checkpoint inhibitors in acute leukemias

Track 13 Role of first- and second-generation hypomethylating agents in MDS

Track 14 Management of MDS and outcomes for patients who experience disease progression with a first-line hypomethylating agent

Select Excerpts from the Interview

Tracks 1-4, 13-14

DR LOVE: Would you discuss current investigation of novel targeted agents for FLT3-mutated acute myeloid leukemia (AML)?

DR KANTARJIAN: FLT3 abnormalities occur in 20% to 30% of patients with AML. During the past 10 years we have tested several FLT3 inhibitors, and now those results are coming to fruition. The randomized Phase III RATIFY trial in front-line FLT3-positive AML was reported at ASH. Patients were randomly assigned to standard 3 + 7 chemotherapy with or without the FLT3 inhibitor midostaurin. A statistically significant improvement in median overall survival was demonstrated among the

patients who received midostaurin, which established the role of FLT3 inhibitors, and we are hoping that midostaurin will be approved soon in this setting (Stone 2015).

One question is whether patients with FLT3 wild-type disease would also benefit from FLT3 inhibitors, because on this study a benefit was evident for patients with FLT3 point mutations, who were not expected to benefit. Crenolanib has the capacity for targeting FLT3 point mutations, so it could expand the role of these agents as they are studied.

Sorafenib, one of the most potent FLT3 inhibitors, is already approved for other indications. The SORAML trial evaluated the addition of sorafenib to standard chemotherapy and demonstrated a significant improvement in event-free survival. No benefit was evident in overall survival because many more patients underwent allogeneic stem cell transplant on the standard-chemotherapy arm (Röllig 2015). However, most of the data suggest that FLT3 inhibitors will become standard therapy.

DR LOVE: What is new and promising in the treatment of myelodysplastic syndromes (MDS)?

DR KANTARJIAN: A couple of areas are promising in MDS, the first being the role of the oral hypomethylating agents, such as oral decitabine and oral azacitidine. They seem to be quite promising and at least as effective as the subcutaneous and IV formulations.

The second area of interest is the development of the second-generation hypomethylating agents. SGI-110, or guadecitabine, which is made up of guanosine and decitabine, might be a positive development in the treatment of MDS. We are proposing studies combining guadecitabine with venetoclax, checkpoint inhibitors, vosaroxin and other agents.

DR LOVE: How do you choose between the hypomethylating agents, and what schedule do you prefer?

DR KANTARJIAN: I believe the 2 hypomethylating agents are equivalent. Azacitidine is administered subcutaneously for 7 days, although one approach of interest is to administer a lower dose for only 4 days, earlier in the course of the disease. Decitabine, which is administered intravenously for 5 days, might be safe and effective when administered for only 3 days. I believe more of these lower doses of the epigenetic therapies will be used in the earlier phases of MDS.

Tracks 5-7

DR LOVE: Any thoughts on the current treatment of acute lymphoblastic leukemia (ALL)?

DR KANTARJIAN: We are witnessing a revolution in adult ALL in 2 areas — monoclonal antibodies that target CD19 and CD22, and chimeric antigen receptor (CAR) T cells. Blinatumomab, a bispecific monoclonal antibody, has yielded marrow CR rates of 40% to 50%. At the 2016 EHA meeting a randomized study was presented that evaluated blinatumomab versus chemotherapy as salvage treatment for ALL and demonstrated a median survival advantage of 7.8 months with blinatumomab versus 4 months with chemotherapy (Topp 2016; [2.1]). I believe this will be an important agent in the treatment of ALL.

2.1

TOWER: Results of a Phase III Study of Blinatumomab for Patients with Relapsed or Refractory Philadelphia Chromosome-Negative B-Cell Precursor Acute Lymphoblastic Leukemia

Efficacy	Blinatumomab (n = 271)	Chemotherapy (n = 134)	Hazard ratio	*p*-value
Median overall survival	7.7 months	4.0 months	0.71	0.011
Complete remission (CR) rate	39%	19%	—	<0.001
CR/CRh/CRi	46%	28%	—	0.001

Select adverse events (Grade ≥3)	Blinatumomab (n = 267)	Chemotherapy (n = 109)
Infection	34%	52%
Neutropenia	38%	58%
Nervous system events	9%	8%
Cytokine release syndrome	5%	0%

CRh = CR with partial hematologic recovery; CRi = CR with incomplete hematologic recovery

Topp M et al. *Proc EHA* 2016;**Abstract S149**.

Data on inotuzumab ozogamicin, another monoclonal antibody, were also presented at the EHA meeting in Europe when we reported on the Phase III INO-VATE ALL study comparing inotuzumab to standard chemotherapy for relapsed/refractory disease (Kantarjian 2016; [2.2]). These data demonstrated a 2-year survival rate of 23% with inotuzumab and 10% with chemotherapy. This is a modest improvement, but I believe

2.2

INO-VATE ALL: Results of a Phase III Study of Inotuzumab Ozogamicin versus Standard Therapy for Relapsed/Refractory B-Cell Acute Lymphoblastic Leukemia

Survival analysis	Inotuzumab (n = 164)	Standard therapy* (n = 162)	Hazard ratio	*p*-value
Median overall survival (OS)	7.7 months	6.7 months	0.77	0.04
2-year OS rate	23%	10%		
Median progression-free survival	5.0 months	1.8 months	0.45	<0.001

Remission (primary ITT analysis)	(n = 109)	(n = 109)	*p*-value
Complete remission rate	80.7%	29.4%	<0.001
Below minimal residual disease threshold	78.4%	28.1%	<0.001
Median duration of remission	4.6 months	3.1 months	0.03

Select Grade ≥3 adverse events	Inotuzumab (n = 139)	Standard therapy (n = 120)
Febrile neutropenia	12%	18%
Veno-occlusive disease	11%	1%
Sepsis	2%	5%
Pneumonia	4%	0%
Pyrexia	1%	1%

ITT = intent to treat; * Investigator's choice of FLAG (fludarabine, cytarabine and granulocyte colony-stimulating factor), cytarabine with mitoxantrone or high-dose cytarabine

Kantarjian HM et al. *N Engl J Med* 2016;375(8):740–53.

that the monoclonal antibodies will continue to be studied in the form of combination therapies for patients with ALL.

In addition, the use of CAR T-cell therapies has generated a lot of excitement. Currently, CAR T cells are all autologous — you take the lymphocytes from the patient, expand them and administer them back to the patient. However, now some companies are evaluating off-the-shelf allogeneic CAR T cells. So in the same way you order blood transfusions and platelet transfusions, in the future we could be ordering CAR T cells, and it would be a major breakthrough if they turned out to be as active as the autologous CAR T cells. Today CAR T cells are used in the salvage setting in ALL. If we cannot cure all or most patients with chemotherapy and monoclonal antibodies, perhaps the addition of CAR T cells at the end of therapy could accomplish this. They are associated with many toxicities, but in the future they could be used in the front-line setting.

Tracks 8-9

DR LOVE: Would you discuss the issue of discontinuing tyrosine kinase inhibitor (TKI) therapy for patients with chronic myeloid leukemia (CML)?

DR KANTARJIAN: I have no doubt that a subset of patients with CML become PCR-negative for durable periods — more than 2 to 3 years — and if you stop therapy, half of these patients will not experience disease recurrence. They are molecularly cured. The question is, do some TKIs induce a higher rate of durable complete molecular cures? And if so, should we be using them rather than generic imatinib, which is an outstanding agent that we hope will be much less expensive?

Generic imatinib is a safe and highly effective BCR-ABL inhibitor for patients with lower-risk CML and patients older than age 60, who could receive it for 10 to 20 years. I believe this agent will play a major role in front-line therapy. However, younger patients or patients with higher-risk CML might benefit from front-line second-generation TKIs in terms of both the potential rate of durable complete molecular response and the chance of discontinuing the treatment to avoid long-term side effects. Receiving treatment for the next 30 to 40 years would bring with it the potential for atherosclerosis, accelerated aging, vaso-occlusive disease and kidney problems.

In addition, my approach is driven by the issue of cost. The prices of the second-generation TKIs continue to increase. That said, these agents are producing a higher incidence of durable complete molecular response, so the second-generation TKIs do bring an advantage if the goal of therapy is durable complete molecular response that results in the discontinuation of therapy. However, you have to spend a lot of money to be able to achieve this. ■

SELECT PUBLICATIONS

Röllig C et al. **Addition of sorafenib versus placebo to standard therapy in patients aged 60 years or younger with newly diagnosed acute myeloid leukemia (SORAML): A multicentre, phase 2, randomised controlled trial.** *Lancet Oncol* 2015;16(16):1691-9.

Stone RM et al. **The multi-kinase inhibitor midostaurin (M) prolongs survival compared with placebo (P) in combination with daunorubicin (D)/cytarabine (C) induction (ind), high-dose C consolidation (consol), and as maintenance (maint) therapy in newly diagnosed acute myeloid leukemia (AML) patients (pts) age 18-60 with *FLT3* mutations (muts): An international prospective randomized (rand) P-controlled double-blind trial (CALGB 10603/RATIFY [Alliance]).** *Proc ASH* 2015;**Abstract 6**.