Monday Night with Research to Practice

Myelodysplastic Syndromes (MDS)/Acute Myeloid Leukemia (AML)

Monday, September 20, 2010

Audience Participant Questions

Q: Where are we regarding combinations of decitabine or azacitidine with other agents?

DR SEKERES: Studies are examining combinations with both decitabine and azacitidine. The combinations could be broadly divided into two major categories.

The first would be the combination of hypomethylating agents with a growth factor — for example, azacitidine or decitabine combined with GCSF, GMCSF, one of the erythropoiesis-stimulating agents or a thrombopoietin analog such as romiplostim. These studies are specifically evaluating the recovery of blood counts so that patients can remain on schedule and receive treatment approximately every four weeks.

The second category involves combining hypomethylating agents with other disease-modifying drugs, such as lenalidomide or HDAC inhibitors. A published study used the combination of azacitidine and lenalidomide in the Phase I setting, and decitabine is also being explored with lenalidomide.

DR KANTARJIAN: The trials of decitabine with HDAC inhibitors did not yield better results, and so far nothing that's added to decitabine has shown superiority. So we are now investigating the alternating sequence of decitabine with clofarabine. In elderly patients with AML, the sequence of clofarabine and low-dose cytarabine, alternating with decitabine, is being investigated.

Q: How long do we have to treat MDS to yield a complete remission?

DR SEKERES: In general, patients who are at lower risk and are being initiated on a therapy should remain on that therapy for at least four months. The therapy could be an erythropoiesis-stimulating agent or a disease-modifying drug. Most studies have indicated that approximately 90 percent of patients who are destined to respond to a drug will do so within those first four months. So it's only a small proportion of patients one would lose by discontinuing the drug at four months.

On the other hand, with patients at higher risk, we have learned from the AZA-001 study that patients remained on azacitidine for a median of nine cycles. Approximately 90 percent of patients who are destined to respond to azacitidine or decitabine will do so within the first six months of therapy. So I generally continue my patients on one of these agents for at least six to nine months of therapy before I declare that the agent does or does not work.

DR KANTARJIAN: The median number of courses to achieve a complete remission is approximately four, so you have to treat for at least four cycles if remission is the goal.

Q: How often do patients develop thrombocytosis while receiving azacitidine? I have two patients with CML/MDS hybrid disorder who received azacitidine in whom platelets have reached up to two million from normal baseline platelet count at initiation.

DR SEKERES: In patients with MDS, if thrombocytosis is seen with azacitidine I can think of two possibilities. The first would be that the patient may have a severe iron deficiency, and the second is that a component of myeloproliferative disorder exists. In these patients, I check for a JAK2 mutation or cMpl expression. We have limited data on the efficacy of MDS agents in patients with such overlap disorders.

DR KANTARJIAN: Usually we don't see severe thrombocytosis in MDS. In a patient with thrombocytopenia, we see improvement and normalization of the platelet counts, but usually we do not see severe thrombocytosis as is described here.

Q: Among patients with MDS with del 5q who are transfusion independent, at what level of Hb would you initiate lenalidomide?

DR SEKERES: This is a great question. With lower-risk MDS, none of the therapies are curative so in the end it is a quality-of-life decision. In such a patient who has MDS with del 5q and is not transfusion dependent or symptomatic, I will hold off on starting lenalidomide until that patient becomes symptomatic or starts to require transfusions.

DR KANTARJIAN: This is a tough question. If what we believe lenalidomide does is correct, that is, it suppresses the del 5q clone, then in the long run one should affect the outcome of such patients with lenalidomide. If a patient with MDS and del 5q has mild anemia without transfusion dependence, one could make the argument to start lenalidomide to induce a complete cytogenetic response or simply wait and watch the patient. If I have such a patient with MDS and del 5q who has anemia without transfusion dependence, I would be inclined to treat in order to achieve a complete cytogenetic response. The reality is, we don't know the answer.

Q: A 63-year-old woman with MDS, an IPSS score of 1.5 and trisomy 8 receives decitabine. After four cycles of decitabine therapy, trisomy 8 normalizes. The patient had allogeneic BMT scheduled after four cycles, but she cancelled for fear of high up-front mortality and change in quality of life. Now she continues cycle five of decitabine. Would BMT be the best recommendation for this patient?

DR SEKERES: No studies exist for patients who are candidates for allogeneic transplantation if we are treating before transplant or taking them straight to transplant. Our practice has been to treat in order to obtain some sort of response and thus they may become better transplant candidates. I believe that in this patient you may want to move forward with the transplant, as decitabine alone will not be curative. Eventually, a patient receiving decitabine will experience relapse, and then we do not have many options to take the patient back into a response prior to transplant. I believe that your patient is in the best situation to move forward with transplant at this time.

Q: What is included in the International Prognostic Scoring System (IPSS)?

DR KANTARJIAN: The IPSS requires three elements. One is the percent of marrow blasts, the second is cytogenetics and the third is the number of cytopenias (Figure 1).

Figure 1 **IPSS in MDS**

	Score value				
Prognostic variable	0	0.5	1.0	1.5	2.0
Bone marrow blasts	<5%	5-10%	—	11-20%	21-30%
Karyotype*	Good	Intermediate	Poor	—	—
Cytopenias	0 or 1	2 or 3	—	—	—

Scores for risk groups: Low = 0; INT-1 = 0.5-1.0; INT-2 = 1.5-2.0; high ≥ 2.0

* Good karyotype = normal, -Y, del 5q, del 20q; poor karyotype = complex (≥3 abnormalities) or chromosome 7 abnormalities; intermediate karyotype = other abnormalities

Greenberg P et al. *Blood* 1997;89(6):2079–88.

Q: How do we prepare patients with MDS who need surgery?

DR SEKERES: If a patient has MDS, in my experience it is rare to see bleeding diathesis outside of that related to thrombocytopenia. Mostly the platelets are functional and are simply numerically low. The way to manage is to transfuse platelets perioperatively. If it is major surgery, then we should aim for platelets close to 100,000/mm^3. For minor procedures, 50,000/mm^3 may suffice.

If a patient with a platelet count of 50,000/mm^3 to 75,000/mm^3 has an enlarged spleen or if the patient has a lot of bruising, then it is likely that the platelets may be dysfunctional. In these situations I would preemptively use platelet transfusions to increase that patient's platelet count to more than 100,000/mm^3.

DR KANTARJIAN: In addition to platelet transfusions, you may also need to educate the patients that they may still develop complications.

Q: Can one make a diagnosis of MDS in a patient with anemia who has no deficiencies, no increase in reticulocyte count and normal-appearing bone marrow?

DR SEKERES: Absolutely not. The diagnosis of MDS requires 10 percent dysplastic cells. I have a handful of patients in whom no dysplasia is evident on bone marrow evaluation, and it is frustrating because clinically it appears as if they may have MDS. One reassuring thing about these patients is that for the most part they don't require therapy. We can wait and repeat the bone marrow exam in a year or two and see if dysplasia eventually develops.

DR KANTARJIAN: No. The *sine qua non* for a diagnosis of MDS requires the presence of dysplastic changes in at least one lineage in the bone marrow. So in normal-appearing bone marrow, one cannot call it MDS.

Q: What is the utility of lenalidomide in transfusion-dependent patients with non-del 5q, low-risk MDS?

DR SEKERES: A large Phase II study that enrolled more than 200 patients, involving transfusion-dependent patients with lower-risk MDS without the deletion 5q abnormality, showed a transfusion-independence rate of 26 percent. So I believe it is something worthwhile to try if you don't have other options.

DR KANTARJIAN: Usually the transfusion-independence rate is approximately 25 percent, and the overall improvement is 30 to 40 percent. The durability of the response is approximately 40 weeks. However, the incidence of complete cytogenetic responses is lower, at less than 10 percent.

Q: How good are we at diagnosing MDS with bone marrow biopsy in community hospitals?

DR KANTARJIAN: Some discordance occurs among pathologists — approximately 20 percent. In general, a good pathologist should be able to make a diagnosis of MDS though it requires a degree of expertise. The discordance rate should be approximately 20 percent among good pathologists too.

Q: Does a role exist for weekly hypomethylating agents in patients with MDS and severe pancytopenia?

DR KANTARJIAN: We evaluated decitabine daily for three days versus weekly for three weeks, and the daily for three days regimen was better. So I would not advocate a weekly dose of hypomethylating agents.

Q: Do you dose reduce azacitidine based on blood counts? Why or why not?

DR KANTARJIAN: In a patient with active disease, I do not reduce the azacitidine dose. If the patient achieves a complete remission and experiences significant cytopenias related to azacitidine, then the dose could be reduced to 50 mg/m^2 daily for seven days or 75 mg/m^2 daily for five days. So only among patients in whom the disease has disappeared should one consider dose reductions. If cytopenias are concomitant with active disease, I usually do not reduce the dose of azacitidine unless I see a life-threatening complication or severe drug-related toxicity.

Q: Does changing to a different hypomethylating agent have any value in resistant cases?

DR SEKERES: If a patient does not respond to an adequate course of therapy with one hypomethylating agent, then that patient will not respond to a different hypomethylating agent.

DR KANTARJIAN: Usually the two drugs are cross resistant, so I would not switch from azacitidine to decitabine or vice versa.

Q: When referring a patient with a single or collective cytopenias, when would you perform a bone marrow biopsy?

DR SEKERES: If a patient has an isolated cytopenia, we can usually figure out what is going on without performing a bone marrow biopsy. Once a person has two or more cytopenias, I believe we're required to perform a bone marrow biopsy.

DR KANTARJIAN: Usually if you have a cytopenia that is persistent and has no explanation of an underlying condition or a drug effect, then you have to perform a bone marrow biopsy. Perhaps you can watch the patient for a brief period, exclude other causes of cytopenia and then perform the bone marrow biopsy. But if you have cytopenias, I would not delay performing a bone marrow biopsy beyond one month or six weeks, in case there is no explanation for the cytopenias.

Q: Do you use FISH and/or cytogenetics in MDS?

DR SEKERES: I use a combination of both cytogenetics and FISH. I believe they add to each other. We had a publication in *Leukemia Research* in which we studied a bunch of patients with distinct cytogenetic abnormalities and listed the percent of patients we diagnosed using metaphase cytogenetics alone and then the additional utility of adding FISH and finally adding array technology — single nucleotide polymorphism arrays. With something like the deletion 5q abnormality, we were able to increase the yield from 30 percent to 39 percent. In general, you can probably increase the yield by five or 10 percent by using additional modalities.

DR KANTARJIAN: No. We usually do cytogenetics alone. We do not use FISH because to do so you need multiple probes, and a certain level of false positivity also occurs with FISH. So I prefer regular metaphase cytogenetics.

Q: How can we obtain clofarabine reimbursement for AML?

DR KANTARJIAN: You can show the published data, and whenever you have one or two peer-reviewed publications the insurance companies accept to pay for it. Several publications are out right now on clofarabine in AML. Two of them are in the *Journal of Clinical Oncology*.

Q: What happened to cladribine with standard 3 + 7?

DR SEKERES: The Polish Adult Leukemia Group has studied cladribine as part of induction chemotherapy, and it is now being considered in the US Cooperative Group trials.

DR KANTARJIAN: It is an effective regimen. The peer-reviewed publication from the study from Poland showing that 3 + 7 with cladribine yields better outcomes than 3 + 7 and fludarabine or 3 + 7 alone is eagerly awaited.

Q: The FAB classification suggests >30 percent blasts is AML. What constitutes the difference between the 20 percent and 30 percent cutoffs, and which one should we use?

DR SEKERES: Our center uses the latest WHO classification, which employs the 20 percent cutoff for AML. That said, if you are debating whether to use agents such as azacitidine or decitabine for these patients, I have considered using hypomethylating agents in my patients with AML who have 20 to 30 percent blasts because these patients were enrolled in the pivotal trials of hypomethylating agents.

DR KANTARJIAN: Patients with 20 to 30 percent blasts are considered to have AML by WHO classification and often receive treatment as such. Now, having said this, older patients with AML do not usually receive intensive chemotherapy, and they could receive low-intensity therapy, including hypomethylating agents. So if these patients are unable to tolerate intensive chemotherapy, then they should be considered for low-intensity therapy, such as a hypomethylating agent or a clofarabine-based combination.

Q: What is the role of gemtuzumab in elderly patients with AML?

DR SEKERES: Unfortunately, the role of gemtuzumab has recently evaporated as the FDA has withdrawn its marketing approval for the drug. A number of physicians across the country are actively trying to convince the FDA that this is a bad decision and to go back on that decision. But right now the role is nonexistent.

DR KANTARJIAN: I believe gemtuzumab has an important role. Unfortunately, the FDA has recommended withdrawing the drug from the market. We are trying to convince the FDA through editorials and a recent publication from the MRC demonstrating the role of gemtuzumab in younger patients, but at this stage the drug has been withdrawn from the market.

Q: Do molecular markers such as FLT3 and NPM1 mutations have any prognostic significance in older patients with AML?

DR SEKERES: We check for FLT3 and NPM1 mutations in our patients with AML who have normal cytogenetics. We also use the tests to help gear recommendations for "postremission" therapy — whether we would continue with chemotherapy or recommend stem cell transplantation.

DR KANTARJIAN: We are beginning to see similar findings in older patients with AML as in younger patients. That is, FLT3 mutation is adverse, and NPM1 mutation may be favorable.