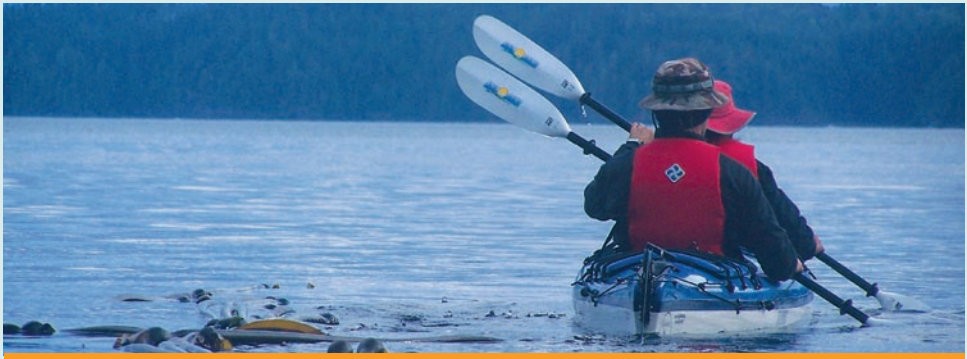
Real-Life Decisions

Clinical Investigators Provide Their Perspectives on the Management of Multiple Myeloma, Myelodysplastic Syndromes and Acute Myeloid Leukemias



Featuring Edited Proceedings and Interviews from a Case-Based Symposium Preceding the 52nd ASH Annual Meeting

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Real-Life Decisions: Clinical Investigators Provide Their Perspectives on the Management of Multiple Myeloma, Myelodysplastic Syndromes and Acute Myeloid Leukemias

A Continuing Medical Education Program

OVERVIEW OF ACTIVITY

The treatment of hematologic cancer remains a challenge for many healthcare professionals and patients despite recent gains made in the management of this spectrum of diseases. Determining which treatment approach is most appropriate for an individual patient requires careful consideration of unique clinical characteristics, physician expertise and available health system resources. To bridge the gap between research and patient care, these proceedings from a case-based CME satellite symposium held at the 2010 American Society of Hematology Annual Meeting, paired with select faculty interviews addressing many of the questions posed by live audience members, attempt to provide the perspectives of clinical investigators on evidence-based care across a diverse set of hematologic cancers. By providing information on the latest research developments and their potential application to routine practice, this activity is designed to assist medical oncologists, hematologists and hematology-oncology fellows with the formulation of up-to-date clinical management strategies for patients with hematologic cancer.

LEARNING OBJECTIVES

- Appraise recent data on therapeutic advances and changing practice standards in acute myeloid leukemia (AML)/acute promyelocytic leukemia (APL) and myelodysplastic syndromes (MDS), and integrate this information into current clinical care when appropriate.
- Apply the results of emerging clinical research to the selection of optimal systemic therapy for patients with newly diagnosed or relapsed or refractory multiple myeloma (MM).
- Develop an algorithm for risk-stratified induction therapy for patients with AML or APL.
- Recall the emerging data with novel agents and combinations in the treatment of MM.
- Offer evidence-based supportive management strategies to facilitate tolerability of and adherence to systemic treatments for AML/APL, MDS and MM.

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INDUCTION THERAPY IN THE TRANSPLANT AND NONTRANSPLANT SETTINGS

DR LOVE: How should cytogenetics be incorporated into clinical decision-making for MM?

DR GERTZ: The high-risk karyotypes are translocations in 4;14 and 14;16, deletion in 17p and gains in 1q. Those are the big, bad prognostic factors.

Why is this important? Because the largest study that compared melphalan and prednisone to bortezomib/melphalan/prednisone for patients with newly diagnosed disease suggested that those bad prognostic features were not significant in the bortezomib-treated population and that bortezomib may neutralize the adverse effect of 4;14 and 14;16 (Mateos 2010). In the relapsed setting, it has been shown that bortezomib again neutralizes the translocations but doesn't appear to have an effect on the 1q gains (Chang 2010). We have used these findings to direct therapy.

For patients who are identified as being at low risk with no genetic or kinetic abnormalities, low-toxicity induction is what we're interested in, and high-dose therapy with transplant will likely provide benefit.

With intermediate disease, such as a translocation 4;14 or 14;16, patients should have bortezomib in line for their treatment.

Patients with deletion 17p — which is the worst prognostic factor — or those who have high labeling index or Ki-67 antigen expression are the patients for whom we start thinking about allogeneic transplant. We use nonmyeloablative transplantation sparingly in our practice, but we don't know what else to do for patients at very high risk.

DR LOVE: What are your thoughts in general about eligibility for and the role of transplant in the era of the novel agents?

DR GERTZ: For patients receiving transplants in the first plateau, we're experiencing a treatment-related mortality rate of one half of one percent, and when we examined patients older than age 65 selected for transplantation, survival was no different than in younger patients. Now, clearly, we don't select as high a percent of patients older than age 65 as we do those younger than age 65, but if we believe they're fit, we're comfortable performing transplant. With all of the available data on the use of novel agents for induction therapy, it's still clear that stem cell transplant will increase the depth of the response — complete response or very good partial response — by an additional 20 percent from about the midforties to the midsixties. So I certainly don't dismiss transplant as a concept based on age alone.

I believe the key message is that transplant is a regimen. It should not be considered the platform on which all myeloma therapy is based, but in the same way that we have two-drug inductions, three-drug regimens

and consolidation and maintenance regimens, stem cell transplant is a regimen. What's controversial is whether it's necessary to perform the transplant up front to maximize survival compared to keeping it as a salvage treatment. But I like to have transplant available as an option, and I certainly do not believe it's rendered obsolete by the presence of the novel agents we have available.

DR LOVE: What is your choice of initial therapy outside of a protocol setting for the patient eligible for transplant?

DR VIJ: I believe you'll get as varied an answer as the number of physicians you have on a panel for this question. Clinical investigators want to identify the "R-CHOP" for myeloma in terms of deepening responses with more intense treatment. Higher complete response rates in the up-front setting have been surrogates for prolonged survival in most trials for myeloma. But I believe we still don't know whether myeloma is going to follow the intermediate-/high-grade lymphoma paradigm or be approached more effectively as a low-grade lymphoma.

In the transplant-eligible population, some studies suggest that bortezomib/thalidomide/dexamethasone (VTD) as a three-drug regimen has better complete response rates and initially improves progression-free survival compared to two-drug regimens (Cavo 2010; [1.1]). That is what is driving my general use of three-drug regimens at the moment.

DR GERTZ: I often use lenalidomide with low-dose dexamethasone (Rd) as induction, but we don't have a one-size-fits-all regimen that's right for every patient. And a big problem is that we have many Phase II trials to refer to. Another issue has to do with the way in which we talk about toxicity. If I talk to you about Grade 3 or Grade 4 neutropenia or thrombocytopenia, most of you, if you're like me, couldn't care less. That will get better in three or four days. When you start talking about Grade 3 or Grade 4 neuropathy, then we're talking about

1.1

Efficacy Results from a Phase III Study of Bortezomib/Thalidomide/Dexamethasone (VTD) versus Thalidomide/Dexamethasone (TD) for Multiple Myeloma: Intent-to-Treat Analysis

	VTD (n = 236)	TD (n = 238)	*p*-value
Response after induction therapy*			
CR	19%	5%	<0.0001
CR + nCR	31%	11%	<0.0001
≥VGPR	62%	28%	<0.0001
≥PR	93%	79%	<0.0001
Three-year progression-free survival	68%	56%	0.0057

CR = complete response; nCR = near complete response; VGPR = very good partial response; PR = partial response

* Responses were centrally reassessed and defined by EBMT criteria.

Cavo M et al. *Lancet* 2010;376(9758):2075-85.

a patient who will be in a wheelchair and perhaps won't get out of the wheelchair. Even when we talk about Grade 2 neuropathy, we say, "Well, it's only Grade 2," but Grade 2 is defined by the fact that it interferes with function. To me, that's a big deal.

DR BENSINGER: It's clear that some of the triplet regimens are highly effective. You can achieve rapid cytoreduction and a rapid decrease in monoclonal protein, but you do pay the price of increased toxicity. Lenalidomide/bortezomib/dexamethasone (RVD) is certainly one of the newer regimens on the block, but it does have a significant incidence of neurotoxicity. I believe you have to be proactive about dose adjusting and being in tune to your patient's symptoms in order to avoid some of these problems.

Of potential relevance to this is a presentation at the 2010 ASH meeting that examined the administration of subcutaneous bortezomib. It was a straightforward trial of intravenous versus subcutaneous bortezomib for patients with relapsed disease receiving a combination of bortezomib and dexamethasone (Moreau 2010). The interesting facet about this trial was that the incidence of neuropathy was reduced by 50 percent, and this may represent a new way to administer this drug.

Off protocol, I generally offer VTD because, although we don't have direct randomized trials, the data after three or four cycles of VTD compared to RVD suggest that VTD is perhaps a more robust combination.

DR LOVE: What about induction therapy for the patient who is not eligible for transplant?

DR BENSINGER: I believe that the data support the use of melphalan/prednisone/thalidomide (MPT) or melphalan/prednisone/bortezomib (MPV). Melphalan/prednisone/lenalidomide (MPR) is another regimen that has been evaluated in a trial with three arms: MP, MPR and MPR with R maintenance. It appears that the winner of that trial is MPR with R maintenance (Palumbo 2010). But the interesting aspect there was that MPR without maintenance therapy was no better than MP.

Good data are also available with the Rd doublet as induction therapy for older patients. The other regimens are used less often for older patients, so I don't believe we have enough data yet.

DR LOVE: We saw more data on Rd versus lenalidomide with high-dose dexamethasone (RD) at ASH 2010. Can you update us on these regimens and the optimal dose of dexamethasone?

DR GERTZ: We know that the response rate is higher with RD, and we know that cardiovascular mortality is lower with Rd (Vesole 2010; Rajkumar 2010). What were the restrictions in this study? If the creatinine was greater than 2.5 mg/dL, patients weren't eligible. If creatinine is higher than 2.5 mg/dL, I don't know if RD and Rd are any different. Also, the early mortality observed is usually in the first four months. But, if you get beyond four months, have you gone past that early mortality risk and now all of the sudden the higher response rate with RD would be justifiable?

I believe it would be a mistake to say that intensive dexamethasone has no

role. Some patients are profoundly cytopenic and can't tolerate any myelosuppressive therapy. Others are beyond initial diagnosis, and those data simply won't apply to patients who've already survived six months into the disease. Finally, the data don't apply to anyone whose creatinine is higher than 2.5 mg/dL.

I believe in selective situations you would ask yourself, "Might this patient be appropriate for treatment with RD?" But for patients with newly diagnosed myeloma and creatinine less than 2.5 mg/dL, I never use high-dose dexamethasone in my practice.

POST-TRANSPLANT MAINTENANCE THERAPY

DR LOVE: What is the current role of post-transplant maintenance therapy in MM?

DR BENSINGER: Many of the current transplant trials have adopted maintenance as a standard in all arms without evaluating a placebo arm or alternative maintenance strategies. I'm concerned because it's unclear whether a survival advantage is truly present.

These drugs come with a cost, both financial and in terms of side effects. Granted, lenalidomide has a low incidence of treatment discontinuation, but patients do experience side effects. Despite a clear advantage in progression-free survival, more cytopenias occurred with the drug during the maintenance period, and more infectious complications were associated with the use of lenalidomide (McCarthy 2010; Attal 2010; [1.2]).

In the absence of compelling survival data, we still have to be cautious about recommending maintenance as a standard treatment after autologous transplant for all patients.

DR VIJ: I tend to agree. I generally have not adopted maintenance for all patients. I am using it for patients who have residual disease, detectable after transplant. I agree that with maintenance therapy, the only endpoint that is meaningful is overall survival.

1.2

Post-Transplant Lenalidomide Maintenance Therapy for Patients with Multiple Myeloma

	IFM 2005-02[1]		CALGB-100104[2]	
	Lenalidomide (n = 307)	**Placebo** (n = 307)	**Lenalidomide** (n = 231)	**Placebo** (n = 229)
Median PFS[1] or TTP[2]	42 mo	24 mo	42 mo	22 mo
Deaths	NR	NR	8%	12%

PFS = progression-free survival; TTP = time to progression; NR = not reported

[1] Attal M et al. *Proc ASH* 2010;**Abstract 310**; [2] McCarthy PL et al. *Proc ASH* 2010;**Abstract 37**.

BONE-TARGETED TREATMENT OF MYELOMA

DR LOVE: Any comments about the MRC study of zoledronic acid?

DR GERTZ: The question about the optimal duration of bisphosphonate therapy underwent a radical change

in the last month. A publication from the MRC in *Lancet Oncology* reported on a thalidomide-based induction regimen followed by stem cell transplant and investigated two bisphosphonates (Morgan 2010; [1.3]). What no one expected was a six-month absolute benefit in survival for the zoledronic acid arm compared to clodronate, an oral bisphosphonate that's not available in the United States. In the design of the study, the plan was to treat to disease progression. If you'd asked the question six months ago, we would have talked about NCCN and ASCO guidelines, which recommend a year or two of bisphosphonates for patients who are responsive and achieve a plateau. But now with the question of a survival advantage with continuous zoledronic acid, you can be certain that all of those cooperative groups are going back to the drawing board to reassess their bisphosphonate recommendations.

DR VIJ: I agree that the MRC study is intriguing. The patients underwent treatment in a somewhat heterogeneous manner, but I believe the power lies in the numbers, close to 2,000 patients. They did show that, independent of skeletal-related events, an improvement in survival was observed with zoledronic acid administered until disease progression. However, I believe that the ASCO guidelines currently state that we should administer bisphosphonates for two years and then stop if the disease is inactive. That is based on the possibility for side effects such as osteonecrosis of the jaw (ONJ) and renal effects with long-term administration.

In this trial, one of the details that came across for the first time was that the rates of ONJ may be in the middle of the range that has been reported in the past. Some have said as low as one percent, and some have said as high as 10 percent. I believe it was closer to the three to five percent range here. Because this is still a dilemma, I personally still follow the ASCO guidelines. ■

1.3

Efficacy and Skeletal-Related Events with Zoledronic Acid (ZOL) versus Clodronate as First-Line Therapy in Multiple Myeloma

Endpoint	Risk reduction (in favor of ZOL)	*p*-value
Overall survival (OS)*	16%	0.0118
OS adjusted for skeletal-related events (SREs)	15%	0.018
Progression-free survival*	12%	0.0179
SREs	24%	0.0004

* Adjusted for chemotherapy and minimization factors

Morgan GJ et al. *Lancet* 2010;376(9757):1989-99; Morgan GJ et al. *Proc ASCO* 2010;**Abstract 8021.**

SELECT PUBLICATIONS

Attal M et al. **Maintenance treatment with lenalidomide after transplantation for MYELOMA: Final analysis of the IFM 2005-02.** *Proc ASH* 2010;**Abstract 310**.

Cavo M et al. **Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: A randomised phase 3 study.** *Lancet* 2010;376(9758):2075-85.

Chang H et al. **Impact of genomic aberrations including chromosome 1 abnormalities on the outcome of patients with relapsed or refractory multiple myeloma treated with lenalidomide and dexamethasone.** *Leuk Lymphoma* 2010;51(11):2084-91.

Mateos MV et al. **Bortezomib plus melphalan and prednisone compared with melphalan and prednisone in previously untreated multiple myeloma: Updated follow-up and impact of subsequent therapy in the phase III VISTA trial.** *J Clin Oncol* 2010;28(13):2259-66.

McCarthy P et al. **Phase III Intergroup study of lenalidomide versus placebo maintenance therapy following single autologous hematopoietic stem cell transplantation (AHSCT) for multiple myeloma: CALGB 100104.** *Proc ASH* 2010;**Abstract 37**.

Moreau P et al. **A Phase 3 prospective randomized international study (MMY-3021) comparing subcutaneous and intravenous administration of bortezomib in patients with relapsed multiple myeloma.** *Proc ASH* 2010;**Abstract 312**.

Morgan GJ et al. **First-line treatment with zoledronic acid as compared with clodronic acid in multiple myeloma (MRC Myeloma IX): A randomised controlled trial.** *Lancet* 2010;376(9757):1989-99.

Palumbo A et al. **A Phase 3 study evaluating the efficacy and safety of lenalidomide combined with melphalan and prednisone in patients ≥ 65 years with newly diagnosed multiple myeloma (NDMM): Continuous use of lenalidomide vs fixed-duration regimens.** *Proc ASH* 2010;**Abstract 622**.

Rajkumar SV et al. **Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: An open-label randomized controlled trial.** *Lancet Oncol* 2010;11(1):29-37.

Vesole D et al. **Lenalidomide plus low-dose dexamethasone (Ld): Superior one and two year survival regardless of age compared to lenalidomide plus high-dose dexamethasone (LD).** *Proc ASH* 2010;**Abstract 308**.

RISK-STRATIFIED MANAGEMENT OF MYELODYSPLASTIC SYNDROMES (MDS)

DR LOVE: For patients with low-risk MDS and a normal karyotype, what do you generally recommend as initial systemic therapy after treatment with erythropoietin?

DR SMITH: If the MDS primarily involves cytopenias of red cells, I believe lenalidomide is the natural next choice. We know that the responses with lenalidomide are erythroid based (List 2006). Given a patient with low-risk disease and red-cell needs for whom you want to try to achieve transfusion independence, lenalidomide is an effective drug. Approximately 25 percent of the time patients become transfusion independent with this agent, and it's well tolerated in this group.

However, for patients with low-risk disease who have more than simply red-cell needs, such as significant other cytopenias, the DNA methyltransferase inhibitor class of drugs can improve trilineage responses with improvements of all cell lines.

DR LOVE: How do you approach the choice of hypomethylating agents?

DR SMITH: Our group at Johns Hopkins often uses 5-azacitidine as our primary drug, in part because

of our familiarity with it, but also because of the AZA-001 data reporting improved survival with this particular agent (Fenaux 2009; [2.1]).

DR RAVANDI: It's impossible to determine the difference between decitabine and 5-azacitidine unless you perform a head-to-head randomized study, and I believe a study such as that is in preparation.

Some preclinical data suggest decitabine may be a more potent DNA methyltransferase inhibitor, but whether that means anything in terms of response and survival remains to be seen.

Studies have shown improvement in survival using 5-azacitidine, whereas the studies with decitabine have been negative in terms of improvement of survival (Wijermans 2008). However, one of the major criticisms with both of the decitabine studies is the low median number of treatment cycles that the patients received. Those of us who use these agents believe that to gain benefit from them, a sufficient number of cycles needs to be administered.

It is important to wait until the patient clearly shows no response after three or four cycles before discontinuing treatment. The median number of cycles administered in at least one of the decitabine studies was only two, which means that 50 percent of patients didn't even have the chance to receive the third cycle.

DR LOVE: For practical purposes, what schedule and method of administration do you recommend when using 5-azacitidine?

DR SMITH: For patients for whom we've established the goal of therapy as improvement in survival, we try to adhere to the seven-day approved regimen. We start patients at 75 mg/m^2, often administered intravenously rather than subcutaneously because many of our patients have semipermanent catheters in place.

We are fortunate to have a clinic that allows us to administer this drug seven days a week. This may be a challenge for some practices (2.2), but when push comes to shove and you have to go to a secondary schedule, we often suggest five days a week because that's practical and easy to deliver.

DR VIJ: We have data on the five-day schedule and on the interrupted Saturday and Sunday regimen mainly for patients with low-risk disease from a community trial that was conducted here in the United States (Lyons 2009). For a patient who has intermediate-2-risk disease or higher, I'm not sure we have the data. We

2.1 **Azacitidine versus Conventional Care Regimens (CCR) for Patients with Higher-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

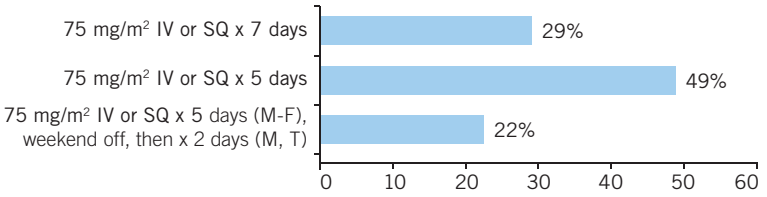
Fenaux P et al. *Lancet Oncol* 2009;10(3):223-32.

2.2

Azacitidine Dosing in Myelodysplastic Syndromes (MDS)

A 68-year-old woman with mild dementia and fatigue presents with pancytopenia (Hgb 9.6 g/dL, WBC 2,000/mm³), a platelet count of 160,000/µL and bone marrow evidence of 25 percent blasts, consistent with high-risk MDS.

If the patient were to receive azacitidine, which initial dose and schedule would you recommend?



Research To Practice Patterns of Care Survey, October 2009 (n = 100 practicing oncologists/hematologists).

2.3

Efficacy of a Five-Day Schedule of Intravenous Azacitidine in a Phase II Trial for Patients with Myelodysplastic Syndromes

	Evaluable patients (n = 22)	Low risk (n = 9)	High risk (n = 13)	*p*-value
Response	27%	33%	23%	0.655
Complete response	23%	33%	15%	
Median PFS (days)	339	357	302	0.053*
Median OS (days)	444	Not reached	304.5	0.027*
Median time to response (days)	108	109	107	Not significant
Median duration of response (days)	450	577.5	302	0.025*

* Low risk (low and intermediate-1) versus high risk (intermediate-2 and high)
PFS = progression-free survival; OS = overall survival

Martin MG et al. *Am J Hematol* 2009;84(9):560-4.

conducted a Phase II nonrandomized trial with intravenous 5-azacitidine administered for five days to a small number of patients. We reported similar response rates to the seven-day regimen but with less durability (Martin 2009; [2.3]).

DR SMITH: Administering treatment to patients with MDS can be done for a number of reasons, such as to enable them to become transfusion independent or to keep their disease from progressing. Additional goals might be to obtain a response and improve survival. So I believe you have to mix and match the goals of the therapy — what you're trying to prevent or achieve for your patient — with the patient's lifestyle and his or her disease. It can be a challenge to sort through those issues with your patients.

DR LOVE: A common question we're asked by oncologists regarding MDS is, "My patient is faring well, so how long do I have to keep the hypomethylating agent going? Can I stretch it out?"

DR VIJ: I believe that we don't have an answer to this from a randomized trial. The designs that were initially used in the pivotal studies allowed patients to discontinue the drug after two cycles of confirmed complete response. Patients achieving only a partial response were required to continue with treatment cycles until disease progression. But in clinical practice, at least at our institution, we are often adopting continuation of treatment for all patients who are at least experiencing hematologic improvement or better beyond six months until disease progression. In my experience, if you stop treatment, you rarely see a response with a rechallenge.

DR FENAUX: In the trial that showed a survival advantage for azacitidine, the median number of cycles was nine for all patients but 15 for patients whose disease responded (Fenaux 2009). I believe that the survival advantage was probably a result of sufficiently long treatment.

DR LOVE: How do you generally care for patients who develop cytopenia while receiving treatment with 5-azacitidine or decitabine?

DR SMITH: For patients with lower-risk disease and lots of cytopenias, I delay the demethylating agent for the next cycle or two. This is to ensure that I'm not inducing too much cytotoxicity and to make sure I don't put the patient in a situation in which they are at risk for infections and other complications.

For patients with higher-risk disease, I'm willing to put up with the cytotoxic effect that induces cytopenias because the goal is to get them through a few rounds of treatment to clear out their bone marrow.

So tolerance of cytopenias may vary based on the individual patients you're caring for and the aggressiveness of their disease.

DR LOVE: Would you discuss the role of chelation therapy in MDS?

DR SMITH: Five years ago I would probably have said we never use chelation therapy. More recently, we've received additional data on the importance of iron overload and the trouble it causes our patients with MDS. In fact, I'm not afraid to start iron chelation any time I'm caring for a patient who has received more than eight to 10 transfusions, provided I believe he or she is going to have an ongoing transfusion need.

I don't believe any benefit is obtained by letting someone reach some arbitrary goal of 20 or 30 packed red cell units. If the patient has active disease and requires ongoing transfusions, I believe chelation makes sense.

Some fascinating data now suggest that patients with better-controlled iron levels tend to fare better in the long term. A lot of investigations are ongoing as to why that may be, but I believe it's worth considering early chelation for patients. We used to believe that trouble arose with iron overload 10 or 15 years down the line. Most of our patients with MDS weren't alive at that point, so it wasn't a pressing issue. ■

SELECT PUBLICATIONS

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.

List AF et al. **Lenalidomide: Targeted anemia therapy for myelodysplastic syndromes.** *Cancer Control* 2006;13(Suppl):4-11.

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.

Martin MG et al. **A phase II study of 5-day intravenous azacitidine in patients with myelodysplastic syndromes.** *Am J Hematol* 2009;84(9):560-4.

Wijermans P et al. **Low dose decitabine versus best supportive care in elderly patients with intermediate or high risk MDS not eligible for intensive chemotherapy: Final results of the randomized Phase III study (06011) of the EORTC Leukemia and German MDS Study Groups.** *Proc ASH* 2008;**Abstract 226**.

DIAGNOSIS AND TREATMENT OF CHRONIC MYELOMONOCYTIC LEUKEMIA (CMML)

DR LOVE: What exactly is CMML, both from a classification and conceptual perspective?

DR SMITH: CMML is a unique and interesting form of myelodysplasia. It's sort of the crossover between MDS and the proliferative disorders. It has features of both, and as such it's never had its own therapeutic approach. In fact, CMML was excluded from the IPSS, the original prognostic scoring system that we all use — so most IPSS scores don't apply to patients with CMML.

DR FENAUX: CMML is difficult to classify — some cases are more myelodysplastic and others are more myeloproliferative and can even occur with extramedullary disease, for which the treatment approach is probably unique. With CMML, you need monocytosis — it should be more than 1,000 and more than 10 percent of the differential to truly be considered diagnostic of CMML.

DR VIJ: Sometimes you don't see them called monocytes by the morphologist, however. He or she may classify them as atypical lymphocytes. I agree that, at least in the pathological literature, the monocytosis is a must. You can have an absence of dysplasia and still call it CMML if it is persistent for three months or more and you cannot determine any other causes of monocytosis.

DR RAVANDI: Some cases of CMML are associated with PDGFR alpha and beta abnormalities and respond to tyrosine kinase inhibitors.

DR LOVE: What proportion of patients with CMML have mutant PDGFR?

DR SMITH: It's a low number, probably less than 10 percent. However, interest has developed because of the good tolerability profile of imatinib, and physicians want to try it.

DR LOVE: How do you approach the younger, otherwise-healthy patient with CMML?

DR FENAUX: Transplant is the ul-

timate goal, but it's been published and it is our experience that intensive chemotherapy works particularly poorly in CMML. The first decision is whether you should transplant up front or do something before, and if I administer something before, it is a hypomethylating agent because we have good data with these agents in this setting (Braun 2010; Costa 2010; [3.1]).

DR SMITH: Allogeneic transplant is potentially curative for patients with CMML, so I believe that considering transplant is correct when you first meet a patient with this disease. The question is, how do you optimize patients and prepare them for transplant?

We know that traditional chemotherapy is quite toxic, particularly for older patients, and it does not confer much benefit in MDS. We have been focusing on the use of DNA methyltransferase inhibitors as front-line therapy.

When patients respond to DNA methyltransferase inhibitors, it appears to be a good bridge to transplant. Obviously, patients whose disease progresses through these treatments must proceed to more intensive-type therapies.

The data with both drugs are interesting in CMML. For many cases of MDS, 5-azacitidine is the DNA methyltransferase inhibitor of choice, based on the positive survival data (Fenaux 2009; [2.1, page 9]).

With decitabine, it turns out that we have data specifically with patients with CMML indicating that they have nice responses to decitabine (Braun 2010; Costa 2010; [3.1]). I believe you can use either of the two drugs for a patient with CMML in whom you're trying to stabilize the disease before moving on to allogeneic bone marrow transplant. ■

3.1

Efficacy of Hypomethylating Agents — Azacitidine in Chronic Myelomonocytic Leukemia (CMML) and Decitabine in Advanced CMML

	Azacitidine (n = 36)[1]	Decitabine (n = 39)[2]
Response*		
Overall response rate	39.0%	38.6%
Complete response (CR)	11.0%	10.3%
Marrow CR	Not reported	20.5%
Partial response	3.0%	Not reported
Hematologic improvement	25.0%	7.7%
Median overall survival	12.0 months	Not reached
Two-year overall survival rate	Not reported	60.0%
Survival, responders vs nonresponders (months)	15.5 vs 9.0 (p-value = 0.04)	Not reported

* Response with azacitidine was by modified International Working Group (IWG) criteria. Response with decitabine was based on IWG 2006.

[1] Costa R et al. *Cancer* 2010;[Epub ahead of print]; [2] Braun T et al. *Proc ASH* 2010;**Abstract 1873**.

SELECT PUBLICATIONS

Braun T et al. **A Phase II study of decitabine in advanced chronic myelomonocytic leukemia (CMML).** *Proc ASH* 2010;**Abstract 1873**.

Costa R et al. **Activity of azacitidine in chronic myelomonocytic leukemia.** *Cancer* 2010;[Epub ahead of print].

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.

Seymour JF et al. **Effects of azacitidine compared with conventional care regimens in elderly (≥ 75 years) patients with higher-risk myelodysplastic syndromes.** *Crit Rev Oncol Hematol* 2010;76(3):218-27.

MANAGEMENT OF ELDERLY PATIENTS AND THOSE WITH POOR-RISK ACUTE MYELOID LEUKEMIA (AML)

DR LOVE: How do you generally approach treatment for older patients with AML or those with poor-risk disease?

DR SMITH: Not many treatment options are available outside of clinical trials for patients with AML who aren't candidates for intensive therapies. We use DNA methyltransferase inhibitors in this setting, and we tend to administer them continually. We know that these drugs take two, three, four or six cycles until we can obtain an objective chance of a good response (Cashen 2010; Fenaux 2010). In general, when I have limited treatment options I tend to lean toward using them until true objective failure.

Also, when you are using these agents for patients with aggressive bone marrow diseases, one of the other goals — aside from a response, of course — is to keep the disease stable and not allow it to become worse. Transfusion needs and quality of life might improve even without an objective bone marrow response.

However, for patients who experience disease progression while receiving a DNA methyltransferase inhibitor who were deemed in the past not to be eligible for intensive chemotherapy, other agents studied more recently include drugs like clofarabine, which has favorable activity in AML. However, it's not considered to be an easy therapy.

In Europe, physicians may use low-dose cytarabine after DNA methyltransferase failure. In the United States we have not been as enthralled with that approach, and I believe it's partly because we're continually trying to find something more effective.

DR RAVANDI: I believe the best treatment for elderly patients with AML is a clinical trial. Unfortunately for the patients you see in practice, many of them won't be able to enroll on any clinical trials. So we have to design studies for that specific group of elderly patients — those who have an expectation of induction death with the standard 3 + 7 chemotherapy regimen, which is as high as 20 to 30 percent, and a low expectation of long-term survival, only about 10 percent.

These patients clearly shouldn't receive

the 3 + 7 regimen, and they need a clinical trial mainly because we haven't made the slightest dent in the outcome of older patients with AML in the past three decades (Kantarjian 2010; [4.1]).

I would categorize agents as having low, intermediate or high intensity. I reserve high-intensity regimens based on traditional chemotherapy for fit older patients with AML. I administer the low-intensity regimens, such as hypomethylating agents, to the patients with poor-risk AML with a high potential for induction mortality. The intermediate-intensity agents, such as clofarabine, may come into the arena in the future.

DR LOVE: Does FLT3 currently play a routine role in AML risk assessment?

DR SMITH: FLT3 is becoming one of the most important and reliable prognostic markers for newly diagnosed AML. FLT3 analysis evaluates for FLT3 internal tandem duplication (ITD). That mutation universally carries an extremely poor prognosis. If you have a patient with an FLT3 mutation who reaches remission and moves on to an allogeneic transplant fairly quickly, it appears that offers a more favorable outcome than delaying transplant.

We have strongly recommended that at diagnosis the first sample of bone marrow be sent off for studies that include traditional cytogenetics and, now, molecular abnormalities such as FLT3 ITD.

We also repeat the testing at the time of relapse, regardless of the patient's status at diagnosis, because a small number of patients who had FLT3 wild-type disease initially may develop FLT3-positive disease by the time of relapse and vice versa. I believe that's an important piece of information, and we highly recommend testing. ■

4.1

Efficacy and Safety with Standard Therapy of Cytarabine and Daunorubicin for Acute Myeloid Leukemia (≥20 Percent Blasts) in Patients 70 Years Old or Older between 1990 and 2008

3 + 7 regimen (n = 430)	Complete response	Mortality 4-wk/8-wk	Median survival	1/2/3-year survival
Outcomes	45%	26%/36%	4.6 months	28%/16%/10%

3 + 7 regimen: Cytarabine 100 to 200 mg/m^2 qd x 5 to 7 days + daunorubicin, 45 to 90 mg/m^2 qd x 3 days

Kantarjian H et al. *Blood* 2010;116(22):4422-9.

SELECT PUBLICATIONS

Cashen AF et al. **Multicenter, phase II study of decitabine for the first-line treatment of older patients with acute myeloid leukemia.** *J Clin Oncol* 2010;28(4):556-61.

Fenaux P et al. **Azacitidine prolongs overall survival compared with conventional care regimens in elderly patients with low bone marrow blast count acute myeloid leukemia.** *J Clin Oncol* 2010;28(4):562-9.

Kantarjian H et al. **Intensive chemotherapy does not benefit most older patients (age 70 years or older) with acute myeloid leukemia.** *Blood* 2010;116(22):4422-9.

TREATMENT OF ACUTE PROMYELOCYTIC LEUKEMIA (APL)

DR LOVE: What factors are used for risk stratification and treatment selection for patients with newly diagnosed APL?

DR SMITH: The best stratification we have for identification of patients at low risk is based on cytopenias. A low white blood cell count and a relatively preserved platelet count tend to put the patient in a low-risk group. Patients with white counts higher than 10,000 or platelet counts lower than 50,000 tend to have worse prognoses.

In terms of how this affects treatment selection, data now suggest Ara-C is likely better in the management of high-risk disease. Additionally, some larger studies from Europe suggest that Ara-C may not be the most important component for patients at low risk (Lo-Coco 2010). The questions on the table right now include, can you get rid of Ara-C, and do you need maintenance strategies for people who truly have low-risk disease?

However, the NCCN guideline panel — which I am a member of for AML — recommends that a team of physicians actively treating APL stick to one of the tried and true approaches and follow it straight through treatment. That is the best way to allow yourself and your patients the best chance of having good results.

With this disease I tell my fellows, "This is the one you call me in the middle of the night for." Although they can handle a lot of the routine new admissions of the general leukemia patients, APL is the disease for which I come in, examine the smear and write the orders for all-trans retinoic acid (ATRA) immediately because to delay the use of ATRA in someone with APL or even someone with suspected APL could prove tragic. It is the most curable leukemia if you can get patients through the first month of therapy when they're at significant risk for either DIC at presentation or differentiation syndrome.

DR LOVE: What about the role of arsenic trioxide (ATO) in APL?

DR SMITH: ATO is not simply for patients with relapsed disease anymore. It should be a part of your primary therapy for patients with APL. Data suggest that patients who receive ATO early in their course of therapy have improved long-term outcomes (Powell 2010). Many groups, including our own, have moved ATO up into the primary therapy setting for patients with APL.

A few studies have evaluated ATRA in combination with ATO as induction, and it's quite effective (Ravandi 2009; Eghtedar 2010; [5.1]). What's missing is long-term follow-up. We have about a year to two years of follow-up in these patients. It's too early to say that these two biologic agents together are as good as or better than traditional approaches.

DR RAVANDI: We have been advocating treating APL without any chemotherapy since 2003, and essentially we have been using ATRA/ATO. In 2009 we reported our second publication on this combination in the *JCO*, and 92 percent of

patients achieved complete responses, with the vast majority achieving durable molecular responses. Recently at ASH we provided an update of the data and the outcomes continue to be notably good with durable responses.

DR FENAUX: In experienced institutions such as MD Anderson, induction with ATO/ATRA has demonstrated good results (Eghtedar 2010; [5.1]).

However, this combination does carry the risk of activation syndrome. When you take into account that most centers see one or two cases of APL a year, I believe the safety and efficacy of this regimen has to be validated on a multicenter basis.

DR LOVE: Do we know what the mechanism of action of ATO is in the treatment of APL?

DR SMITH: We know that patients who receive treatment with ATO run the risk of differentiation syndrome. Thus it is theorized that part of the mechanism of action of this drug is through a differentiation pathway.

Much interest has been shown in research evaluating how this drug can uncouple the chaperone protein nature of the PML/RAR alpha fusion gene. One mechanism of action of ATO might be that it uncouples this chaperone protein, thus making the cells more vulnerable to death. ■

5.1

Clinical Response and Incidence of Secondary Neoplasms in Patients with Acute Promyelocytic Leukemia Treated with All-Trans Retinoic Acid (ATRA) in Combination with Chemotherapy or Arsenic Trioxide (ATO)

	ATRA with chemotherapy (n = 54)	ATRA with ATO (n = 106)	*p*-value
Clinical response	94.4%	99.0%	Not reported
Secondary neoplasms (%)*	9 (16.7%)	2 (1.9%)	0.29, adjusted for unit time exposure

* Median follow-up time: ATRA with chemotherapy = 136 months; ATRA with ATO = 29 months

Eghtedar A et al. *Proc ASH* 2010;**Abstract 1085**.

SELECT PUBLICATIONS

Eghtedar A et al. **Incidence of secondary neoplasms in patients with acute promyelocytic leukemia treated with all-trans-retinoic acid (ATRA) with chemotherapy or with arsenic trioxide (ATO).** *Proc ASH* 2010;**Abstract 1085**.

Lo-Coco F et al. **Front-line treatment of acute promyelocytic leukemia with AIDA induction followed by risk-adapted consolidation for adults younger than 61 years: Results of the AIDA-2000 trial of the GIMEMA Group.** *Blood* 2010;116(17):3171-9.

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.

Ravandi F et al. **Effective treatment of acute promyelocytic leukemia with all-trans-retinoic acid, arsenic trioxide, and gemtuzumab ozogamicin.** *J Clin Oncol* 2009;27(4):504-10.

POST-TEST

Real-Life Decisions: Clinical Investigators Provide Their Perspectives on the Management of Multiple Myeloma, Myelodysplastic Syndromes and Acute Myeloid Leukemias

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Phase III results comparing thalidomide/dexamethasone (TD) to bortezomib/thalidomide/dexamethasone (VTD) as induction therapy before and consolidation therapy after double autologous stem cell transplantation in newly diagnosed MM reported no improvement in response rates or progression-free survival with the three-drug VTD combination.**
   a. True
   b. False

2. **In the Phase III study evaluating melphalan/prednisone (MP) versus MP with lenalidomide (MPR) versus MPR followed by lenalidomide maintenance (MPR-R) for elderly patients with MM, which regimen resulted in the highest overall response rate?**
   a. MP
   b. MPR
   c. MPR-R

3. **A presentation at ASH 2010 comparing subcutaneous and intravenous administration of bortezomib for patients with relapsed MM reported the incidence of neuropathy was reduced by _____ with subcutaneous bortezomib administration.**
   a. 10 percent
   b. 30 percent
   c. 50 percent

4. **Lenalidomide is an effective option for treating low-risk MDS with cytopenias of red cells.**
   a. True
   b. False

5. **Which of the following hypomethylating agents has shown a survival advantage in the initial management of MDS?**
   a. Azacitidine
   b. Decitabine
   c. Both of the above
   d. None of the above

6. **In the AZA-001 trial, treatment with azacitidine improved median overall survival by approximately _____ compared to conventional care regimens for patients with high-risk MDS.**
   a. Three months
   b. Nine months
   c. 12 months

7. **A Phase II trial reported by Martin and colleagues evaluating intravenous 5-azacitidine administered for five days reported similar response rates to the 5-azacitidine seven-day regimen.**
   a. True
   b. False

8. **A Phase II study of decitabine in advanced CMML reported a two-year overall survival rate of _____.**
   a. 20 percent
   b. 40 percent
   c. 60 percent

9. **In a study of patients with APL treated with ATRA in combination with chemotherapy versus ATRA in combination with ATO, use of the nonchemotherapy regimen of ATRA and ATO was not associated with a higher incidence of secondary cancer.**
   a. True
   b. False

10. **A randomized Phase III study is comparing _____ with ATRA to standard ATRA and anthracycline-based chemotherapy for patients with newly diagnosed APL.**
    a. Ara-C
    b. ATO
    c. Gemtuzumab

Post-test answer key: 1b, 2c, 3c, 4a, 5a, 6b, 7a, 8c, 9a, 10b

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Real-Life Decisions: Clinical Investigators Provide Their Perspectives on the Management of Multiple Myeloma, Myelodysplastic Syndromes and Acute Myeloid Leukemias

Research To Practice is committed to providing valuable continuing education for oncology clinicians, and your input is critical to helping us achieve this important goal. Please take the time to assess the activity you just completed, with the assurance that your answers and suggestions are strictly confidential.

PART ONE — Please tell us about your experience with this educational activity

How would you characterize your level of knowledge on the following topics?

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

	BEFORE	AFTER
Selection, duration of use and administration of hypomethylating agents for the treatment of MDS	4 3 2 1	4 3 2 1
Initial treatment options for APL	4 3 2 1	4 3 2 1
Duration of and benefits from bisphosphonate therapy in MM	4 3 2 1	4 3 2 1
Incorporation of proteasome inhibitors and IMiDs® into induction and maintenance therapy strategies for MM	4 3 2 1	4 3 2 1

Was the activity evidence based, fair, balanced and free from commercial bias?

☐ Yes ☐ No

If no, please explain: .....

Please identify how you will change your practice as a result of completing this activity (select all that apply).

☐ This activity validated my current practice; no changes will be made
☐ Create/revise protocols, policies and/or procedures
☐ Change the management and/or treatment of my patients
☐ Other (please explain): .....

If you intend to implement any changes in your practice, please provide one or more examples:

.....

The content of this activity matched my current (or potential) scope of practice.

☐ Yes ☐ No

If no, please explain: .....

Please respond to the following learning objectives (LOs) by circling the appropriate selection:

4 = Yes 3 = Will consider 2 = No 1 = Already doing N/M = LO not met N/A = Not applicable

As a result of this activity, I will be able to:

- Appraise recent data on therapeutic advances and changing practice standards in acute myeloid leukemia (AML)/acute promyelocytic leukemia (APL) and myelodysplastic syndromes (MDS), and integrate this information into current clinical care when appropriate . . . . . 4 3 2 1 N/M N/A
- Apply the results of emerging clinical research to the selection of optimal systemic therapy for patients with newly diagnosed or relapsed or refractory multiple myeloma (MM). . . . . 4 3 2 1 N/M N/A
- Develop an algorithm for risk-stratified induction therapy for patients with AML or APL . . . . . 4 3 2 1 N/M N/A
- Recall the emerging data with novel agents and combinations in the treatment of MM . . . . . 4 3 2 1 N/M N/A
- Offer evidence-based supportive management strategies to facilitate tolerability of and adherence to systemic treatments for AML/APL, MDS and MM . . . . . 4 3 2 1 N/M N/A

Please describe any clinical situations that you find difficult to manage or resolve that you would like to see addressed in future educational activities:

.....

Would you recommend this activity to a colleague?

☐ Yes ☐ No

If no, please explain:.....

Additional comments about this activity:

.....

As part of our ongoing, continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey.

☐ Yes, I am willing to participate in a follow-up survey.
☐ No, I am not willing to participate in a follow-up survey.

PART TWO — Please tell us about the faculty and moderator for this educational activity

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

Faculty	Knowledge of subject matter	Effectiveness as an educator
William I Bensinger, MD	4 3 2 1	4 3 2 1
Pierre Fenaux, MD	4 3 2 1	4 3 2 1
Morie A Gertz, MD	4 3 2 1	4 3 2 1
Farhad Ravandi, MD	4 3 2 1	4 3 2 1
B Douglas Smith, MD	4 3 2 1	4 3 2 1
Ravi Vij, MD	4 3 2 1	4 3 2 1
Moderator	**Knowledge of subject matter**	**Effectiveness as an educator**
Neil Love, MD	4 3 2 1	4 3 2 1

Please recommend additional faculty for future activities:

.....

Other comments about the faculty and moderator for this activity:

.....

REQUEST FOR CREDIT — Please print clearly

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Professional Designation:

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Hematologic Oncology™ UPDATE

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