

Rounds with the Investigators

Challenging Cases in Multiple Myeloma,
Myelodysplastic Syndrome/Acute Myeloid
Leukemia and Chronic Myeloid Leukemia



Proceedings from a Satellite Symposium Preceding the 51st ASH Annual Meeting

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Rounds with the Investigators: Challenging Cases in Multiple Myeloma, Myelodysplastic Syndrome/Acute Myeloid Leukemia and Chronic Myeloid Leukemia

A Continuing Medical Education Program

OVERVIEW OF ACTIVITY

Beyond the increasingly common non-Hodgkin lymphomas, multiple myeloma (MM), the myeloid leukemias (acute and chronic myeloid leukemia) and high-risk myelodysplastic syndromes (MDS) compose a substantial segment of the adult hematologic cancers encountered in community oncology practice. Thus, evolving treatment paradigms that accompany the recent explosion of active novel therapies must be recognized not only by the academic specialist but also by the general medical oncologist who routinely establishes the initial diagnosis and clinical management plan. To bridge the gap between research and patient care, these proceedings from a case-based CME satellite symposium at the 2009 American Society of Hematology Annual Meeting utilize the perspectives of clinical investigators, in addition to the interactive exchange between these individuals, to apply evidence-based concepts to routine clinical care. By providing access to the latest research developments and expert opinions on these diseases, this activity will assist medical oncologists, hematologists and hematology-oncology fellows in the formulation of up-to-date clinical management strategies for MM, MDS/acute myeloid leukemia (AML) and chronic myeloid leukemia (CML).

LEARNING OBJECTIVES

- Appraise recent data on therapeutic advances in MM, MDS and the myeloid leukemias, and apply this information to clinical practice.
- Identify patients with MM who may benefit from high-dose chemotherapy with stem cell transplantation, and select induction regimens that optimize initial response and long-term outcome.
- Develop an algorithm for the risk-stratified induction treatment of MDS.
- Compare and contrast the benefits and risks of imatinib dose escalation versus alternative tyrosine kinase inhibitor therapy for patients with CML and evidence of residual disease.
- Use prognostic and predictive clinical and molecular markers to aid in treatment decision-making for MM, MDS and the myeloid leukemias.
- Assess the role of maintenance or consolidation treatment approaches in the management of AML.
- Recall the emerging data for novel agents and combinations that may affect the current or future treatment of relapsed MM, MDS, AML or CML.

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MYELODYSPLASTIC SYNDROME (MDS)/ACUTE MYELOID LEUKEMIA (AML)

Case discussion

A 78-year-old man was found to have pancytopenia on a preoperative evaluation for surgery for BPH and was diagnosed with INT-1 MDS with no excess blasts and normal cytogenetics (from the practice of Margaret A Deutsch, MD).

RISK STRATIFICATION AND CLINICAL INDICATIONS FOR INITIATING SYSTEMIC THERAPY IN MDS

► **DR DEUTSCH:** This patient was initially asymptomatic from pancytopenia and had good performance status.

► **DR LOVE:** Gail, when would you start systemic therapy for a patient with MDS?

► **DR ROBOZ:** In all MDS cases, the physician must make an initial decision about when to initiate treatment and what the clinical problem is that needs to be solved. Different questions to consider will include, are we trying to get rid of the disease — which is extremely difficult — or are we trying to improve blood counts?

Does the patient have symptoms from cytopenias or is the patient transfusion dependent? Will the disease be transforming into AML soon? Do we have time to see what will happen or do we need to try something now? This patient is asymptomatic without excess blasts or bad cytogenetics, and watching him initially could be an

acceptable strategy.

► **DR GIAGOUNIDIS:** I agree completely. It is essential to conduct a prognostic assessment with IPSS. This patient has three cytopenias, which gives him 0.5 points. In the absence of excess blasts and with normal cytogenetics, his point total on the IPSS scale is 0.5, which places him in the intermediate-1 IPSS category, and the median overall survival time is 3.5 years.

He is 78 years old, and the median survival in a healthy population of this age is approximately seven years. So he is not losing much of his lifetime.

► **DR DEUTSCH:** The patient was initially observed without treatment. Over the next several months, he became red blood cell transfusion dependent and started receiving darbepoetin. He experienced no response to darbepoetin, his thrombocytopenia worsened and his platelet count dropped from 87,000 to 30,000/ μ L.

THERAPEUTIC OPTIONS FOR ELDERLY PATIENTS WITH LOW-RISK MDS

► **DR LOVE:** What would you consider for this patient at this point, Ari?

► **DR GIAGOUNIDIS:** In Europe, we can't offer azacitidine or decitabine to patients at low risk. Outside of a

clinical trial, I may observe him or administer valproic acid.

► **DR LOVE:** Gail, if you were going to use a hypomethylating agent, which dose and schedule would you use?

► **DR ROBOZ:** The strongest survival data come from the study in patients with INT-2 and high-risk MDS in which azacitidine was administered at 75 mg/m² subcutaneously for seven days (Fenaux 2009; [1.1]). An alternate azacitidine regimen with a five-day schedule (Lyons 2009; Martin 2009) has also included lower-risk disease

and looked good. I wouldn't have any objections to trying the five-day schedule for this 78-year-old patient.

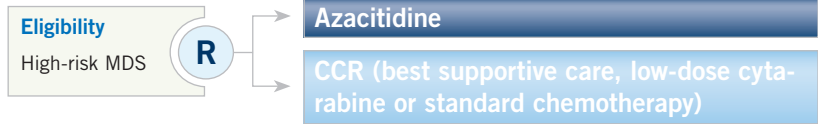
► **DR LOVE:** So do you administer azacitidine on a five-day schedule in your practice outside of a protocol setting (1.2)?

► **DR ROBOZ:** Yes, I often try a five-

1.1

AZA-001: Azacitidine versus Conventional Care Regimens (CCR) for Patients with High-Risk Myelodysplastic Syndromes

Protocol ID: AZA-001
Accrual: 358 (Closed)



	Azacitidine (n = 179)	CCR (n = 179)
Median overall survival	24.5 months	15 months
	HR (95% CI) = 0.58 (0.43-0.77), p = 0.0001	
Median time to AML	17.8 months	11.5 months
	HR (95% CI) = 0.50 (0.35-0.70), p < 0.0001	

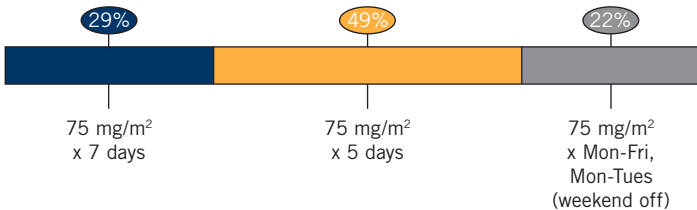
HR = hazard ratio; CI = confidence interval; AML = acute myeloid leukemia

“At 2 years, on the basis of Kaplan-Meier estimates, 50.8% (95% CI 42.1-58.8) of patients in the azacitidine group were alive compared with 26.2% (18.7-34.3) in the conventional care group (p < 0.0001).”

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

1.2

If this patient received azacitidine, which initial dose and schedule would you recommend?



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day schedule for a patient with lower-risk MDS.

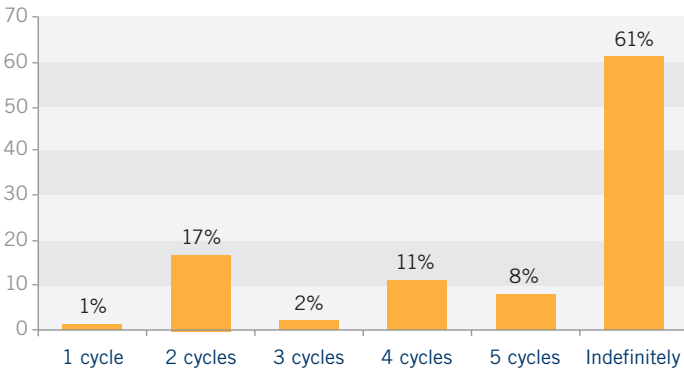
We do like to follow the seven-day schedule in patients with higher-risk disease. I did not have much luck with administering the drug using

subcutaneous injections and prefer the IV approach.

Some patients prefer the IV approach, and we should not make assumptions about what patients will prefer.

1.3

(Dr Deutsch's patient) Azacitidine was administered 75 mg/m² per day SQ x 5 days q4wk. The patient became transfusion independent after 4 cycles of treatment (Hgb 9.5 g/dL, platelet count 50,000/μL). How much longer would you continue the azacitidine?



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DURATION OF AZACITIDINE THERAPY FOR PATIENTS WITH MDS

▶ **DR LOVE:** Ari, how do you approach the issue of duration of treatment with azacitidine in MDS (1.3)?

▶ **DR GIAGOUNIDIS:** We generally continue indefinitely, and I would

stick to schedules of every four to five weeks.

If that's impossible because the patient complains, then go to every six or seven weeks but not beyond that.

Case discussion

A 59-year-old woman in good general health presents with an upper respiratory infection and pancytopenia and is diagnosed with AML with normal cytogenetics (from the practice of Michael A Schwartz, MD).

INITIAL THERAPY FOR A PATIENT WITH AML AND A GOOD PERFORMANCE STATUS

▶ **DR LOVE:** Ari, so what would you be thinking in terms of therapy?

▶ **DR GIAGOUNIDIS:** I would want to know the NPM1 and FLT3 statuses.

► **DR SCHWARTZ:** We did not have those for initial induction but we did send for them subsequently. The results were positive for FLT3 tandem duplication.

► **DR GIAGOUNIDIS:** I would offer

her standard induction therapy with “3+7.” Though she has the same probability of remission, she is at a higher risk for relapse and we would consider allogeneic transplant as an option in the postremission setting.

PERSPECTIVES ON ANTHRACYCLINE DOSE INTENSIFICATION IN AML

► **DR LOVE:** Gail, would you discuss the recent paper by Fernandez et al in *The New England Journal of Medicine* on anthracycline dose intensification for patients with AML?

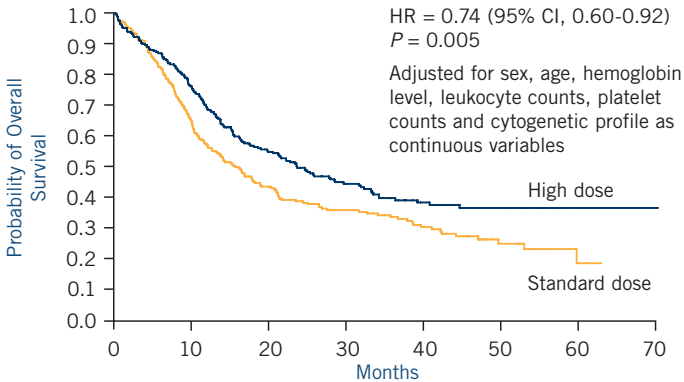
► **DR ROBOZ:** This was a nicely conducted study that showed the higher dose of daunorubicin at 90 mg/m² to be superior to the 45-mg/m² dose (Fernandez 2009; [1.4]). The problem with the study is that the control dose of 45 mg/m² is lower than the dose many physicians use for AML, 60 mg/m².

The question is, for a patient such as this one, would I administer 90 mg/m² instead of 60 mg/m²? I probably wouldn't because I'm not accustomed to it and no particular data set drives me to use that dose.

► **DR GIAGOUNIDIS:** A German study performed in the early 1990s by Thomas Büchner compared the effect of daunorubicin 60 mg/m² to that of 45 mg/m² in a population of patients older than age 60, and higher response rates were achieved with the 60-mg/m² dose (Hiddemann 1999).

1.4

Efficacy of Anthracycline Dose Intensification for Patients with Acute Myeloid Leukemia



Induction Treatment	Total	Deaths	Censored	Median Survival
Standard dose (45 mg/m ³ /day)	330	199	131	15.7 mo
High dose (90 mg/m ³ /day)	327	168	159	23.7 mo

} p-value = 0.003

With permission from Fernandez HF et al. *N Engl J Med* 2009;361(13):1249-59. © 2009 Massachusetts Medical Society. All rights reserved.

So the important points are to push the patients into a complete remission. I don't know whether 90 mg

is better than 60, but 60 is certainly better than 45. I would stick with the 60-mg/m² dose.

RECOMMENDED MOLECULAR DIAGNOSTIC STUDIES IN AML

► **DR ROBOZ:** An international cooperative study is now accruing patients such as this one through the CALGB, incorporating an FLT3 inhibitor into induction therapy for patients with FLT3-positive disease (NCT00651261).

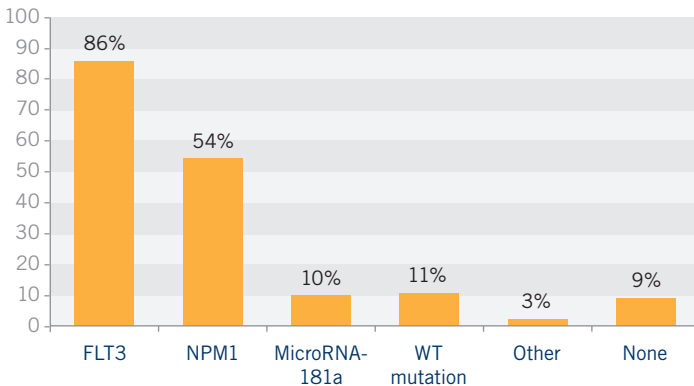
The updated AML guidelines published recently in *Blood* suggest

that for current AML therapy, sending for the molecular diagnostics is no longer a “maybe” — you should order these assays (Dohner 2010).

► **DR LOVE:** We asked about that in our survey, and though most doctors are ordering FLT3, only about half are ordering NPM1 assays (1.5).

1.5

Which molecular studies do you usually recommend for a patient with AML and normal cytogenetics?



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Case discussion

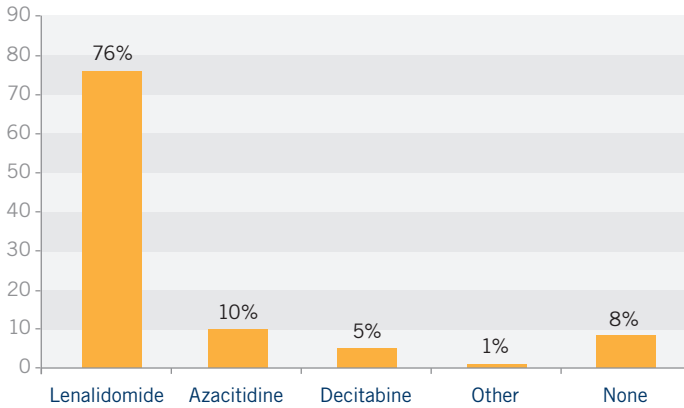
A 93-year-old man with clinically diagnosed MDS becomes transfusion dependent, and a subsequent bone marrow examination confirms MDS with del(5)(q15q33) (from the practice of Robert A Moss, MD).

LENALIDOMIDE IN MDS WITH AND WITHOUT 5Q DELETION

► **DR MOSS:** We started the patient on lenalidomide initially at 10 mg. His blood counts dropped to extremely low levels before starting to increase,

and I reduced the dose to 5 mg during that time. After that, he fared well. He became transfusion independent, and the hemoglobin level

(Dr Moss's case) Which treatment would you recommend for this patient?



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increased to 12.7 g/dL. Although his numbers are better and he no longer requires transfusions, he looks and feels about the same, so he often skips his lenalidomide.

► **DR ROBOZ:** This case demonstrates that for some patients, you can bring up the hemoglobin level significantly and it doesn't matter. They don't jump out of the chair and feel better.

► **DR GIAGOUNIDIS:** Lenalidomide is a surprising drug. It has been observed that 67 percent of patients who have isolated 5q deletion and less than five percent blasts become transfusion independent (1.7).

This gentleman did not appear to benefit much from the treatment as far as the symptoms are concerned, but he became transfusion independent. So I believe he has benefited from lenalidomide therapy, and I would have used the same approach.

► **DR LOVE:** Gail, would you discuss the use of lenalidomide for patients

without 5q deletion?

► **DR ROBOZ:** The initial study was performed in a population of patients at lower risk. Approximately 25 percent of the patients experienced a significant response in hemoglobin levels (1.7). That response rate suggests that further exploration is required. If we could predict in advance who would respond, that would be a significant improvement over trial and error.

Some studies are attempting to use predictive signatures to select in advance the patients who will respond. Most of the data suggest that if a response occurs, it will probably occur within approximately the first 12 weeks.

So if you're trying lenalidomide for a patient who's at low risk and does not have a 5q deletion, the patient does not have to be receiving therapy indefinitely before you decide whether it's providing a benefit. ■

Erythroid Response to Lenalidomide in Myelodysplastic Syndromes (MDS) with Chromosome 5q Deletion and Karyotypes Other than Deletion 5q

	MDS with 5q deletion ¹ (n = 148)	MDS with karyotypes other than deletion 5q ² (n = 214)
Erythroid response		
Transfusion independence	67%	26%
≥50% decrease in number of transfusions	9%	17%
Total transfusion response	76%	43%
Median time to transfusion independence (range)	4.6 weeks (1-49)	4.8 weeks (1-39)
Hemoglobin		
Baseline*, median (range)	7.8 g/dL (5.3-10.4)	8.0 g/dL (6.1-10.6)
Response†, median (range)	13.4 g/dL (9.2-18.6)	11.6 g/dL (7.3-18.0)
Increase, median (range)	5.4 g/dL (1.1-11.4)	3.2 g/dL (1.0-9.8)

* Baseline hemoglobin concentration was the minimum value during the baseline period.

† Response hemoglobin concentration was the maximum value during the transfusion-independent response period.

¹ List A et al. *N Engl J Med* 2006;355(14):1456-65; ² Raza A et al. *Blood* 2008;111(1):86-93.

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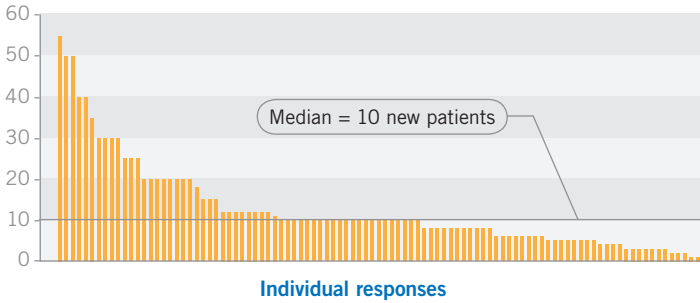
Mohr B et al. **The response to lenalidomide of myelodysplastic syndrome patients with deletion del(5q) can be sequentially monitored in CD34+ progenitor cells.** *Haematologica* 2009;94(3):430-1.

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MULTIPLE MYELOMA (MM)

2.1

How many new patients per year do you see with active multiple myeloma requiring treatment?



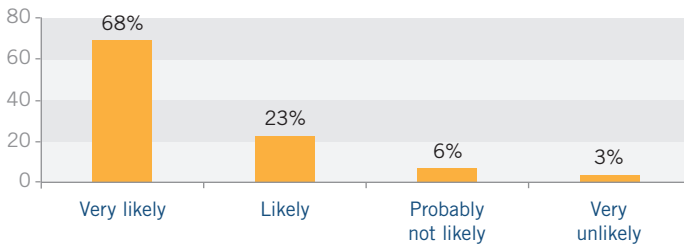
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Case discussion

A 60-year-old man with a history of coronary artery bypass surgery, hypertension, hyperlipidemia and type 2 diabetes is diagnosed with light-chain-only multiple myeloma (from the practice of William N Harwin, MD).

2.2

How likely would you be to pursue a transplant strategy with this patient?



Research To Practice Satellite Symposium, December 4, 2009: Rounds with the Investigators. Results of audience polling (N = 231).

CARDIAC COMORBIDITY AND TRANSPLANTATION IN MM

► **DR LOVE:** Ed, does the history of coronary disease enter into your thinking about treatment for this patient?

► **DR STADTMAUER:** I don't use medical history too much to make the treatment decision. Rather, I consider the patient's true functional

status. I study patients closely to determine whether they have fluid overload, angina or evidence of coronary artery disease. I also check

a MUGA scan or an echocardiogram, and if it's okay, even with that history I'll proceed with appropriate, aggressive therapy.

BORTEZOMIB/LENALIDOMIDE-CONTAINING TRIPLET AND QUADRUPLET INDUCTION THERAPY

► **DR STADTMAUER:** This is a relatively young man, so I feel enthusiastic about the newer agent combinations such as lenalidomide/dexamethasone (RD), bortezomib/dexamethasone and lenalidomide/bortezomib/dexamethasone (RVD). Then I would consider high-dose melphalan with stem cell transplant, if he's tolerating the initial therapy relatively well.

► **DR LOVE:** Dave, how do you feel about these newer regimens?

► **DR VESOLE:** Currently the feeling is that "more is better." Doublets are essentially out the window in some people's minds, and triplets are almost old hat because now we have quadruplets involving bortezomib, lenalidomide, dexamethasone, cyclophosphamide and liposomal doxorubicin. We obtain higher response rates with these regimens but also higher rates of adverse events.

► **DR LOVE:** What was the toxicity profile in Richardson's Phase I/II study of RVD for patients with newly diagnosed MM?

► **DR VESOLE:** I participated in that trial, and we found RVD to be generally well tolerated (Richardson 2009). Still, more toxicity occurs with any three-drug regimen than with two drugs only. It's debatable how statistically significant that is, but we still have to deal with quality of life for these patients who are ultimately not cured of their disease.

► **DR LOVE:** Bill, what happened with this patient?

► **DR HARWIN:** He was referred to the Moffitt Cancer Center in Tampa and received lenalidomide and dexamethasone 40 mg weekly for seven cycles. His free serum kappa light chains completely normalized. He received filgrastim and cyclophosphamide to mobilize stem cells, but he developed a myocardial infarction. Reportedly, his cardiac catheterization was normal, so it was thought that he had a spasm or a transient clot.

They were not able to mobilize his stem cells, but he recovered uneventfully. Approximately three months later he underwent a second attempt to collect stem cells and underwent an autologous stem cell transplantation with melphalan 200 mg/m². He recovered well, is currently not experiencing symptoms and is receiving zoledronic acid alone.

► **DR LOVE:** Ed, do you believe the cardiac event was related to his treatment?

► **DR STADTMAUER:** Obviously, this man has diabetes and coronary artery disease, and certainly those are enough risk factors to cause this cardiac event. By the time they were harvesting his stem cells, he was no longer receiving the lenalidomide and dexamethasone. Certainly, the combination of IMiDs[®] and steroids can increase the risk for thrombosis

(Rajkumar 2010; [2.3]), but I assume he was taking aspirin at that time,

so that was probably not a major contributing factor.

2.3

Rates of Grade III or Higher Toxicity with Lenalidomide and High-Dose (RD) versus Low-Dose (Rd) Dexamethasone as Initial Therapy for Newly Diagnosed Multiple Myeloma

	RD (n = 223)	Rd (n = 220)	p-value
Nonhematologic			
Deep vein thrombosis or pulmonary embolism	26%	12%	0.0003
Infection or pneumonia	16%	9%	0.04
Hypercalcemia	11%	6%	0.09
Cardiac ischemia	3%	0.45%	0.07
Atrial fibrillation or flutter	3%	0.45%	0.12

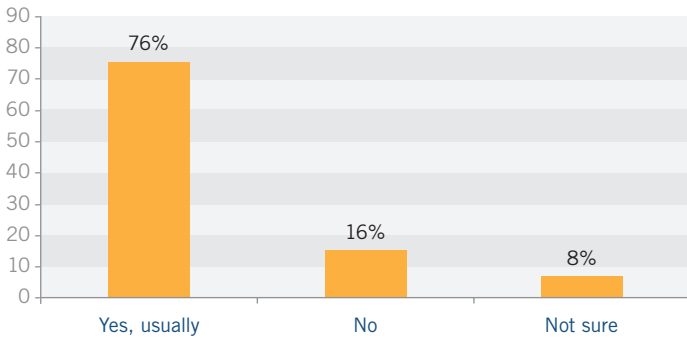
Rajkumar SV et al. *Lancet Oncol* 2010;11:29-37.

Case discussion

A 49-year-old man presents with a 15-cm chest wall mass, large pleural effusion and a collapsed lung. Skeletal survey reveals a solitary lytic lesion in the sixth rib, bone marrow evaluation is normal and blood tests show an IgG kappa M protein of 3.3 g/dL. Needle biopsy of the mass demonstrates plasmacytoma (from the practice of Dr Moss).

2.4

Does this patient have multiple myeloma?



Research To Practice Satellite Symposium, December 4, 2009: Rounds with the Investigators. Results of audience polling (N = 155)

DIAGNOSIS AND TREATMENT OF PLASMACYTOMA

► **DR LOVE:** Ed, does this patient have myeloma?

► **DR STADTMAUER:** He has a cancerous plasma cell disorder that

is the largest plasmacytoma I've ever seen, and the likelihood is high that he has cancerous plasma cells beyond this mass. I would say that by definition he doesn't yet have MM.

I believe that a subset of patients with solitary plasmacytomas are truly healed or cured for the long term. I would order a PET scan, and if it lights up only in this area, then at least I have hope that it's a solitary disease that's simply massive in size.

Also, a normal albumin level would suggest that this might be a solitary plasmacytoma. We tend to see immune paresis and low albumin levels in patients who have more systemic disease.

► **DR VESOLE:** In addition to the PET scan, I would order an MRI of his entire body to determine whether any other focal lesions are present or whether this is truly a solitary plasmacytoma.

► **DR LOVE:** What treatment would you offer to this patient, Ed?

► **DR STADTMAUER:** I would probably treat with systemic therapy initially, to determine whether we could yield a rapid lysis of this mass and seek maximum shrinkage. However, radiation therapy would be the focus of therapy. Then, for a young patient we would consider maintenance or consolidation therapy for residual disease, with high doses of melphalan and potentially a stem cell transplant.

► **DR MOSS:** This patient had no insurance, and that limited our options. Fortunately, he was eligible for the UPFRONT trial, which evaluated bortezomib/dexamethasone versus bortezomib/thalidomide/dexamethasone versus bortezomib/melphalan/prednisone (2.5).

He received bortezomib/melphalan/prednisone and experienced essentially a complete response.

2.5

UPFRONT Study: Interim Efficacy Data from a Phase IIIb Trial Evaluating Three Bortezomib-Based Regimens for Elderly Patients with Newly Diagnosed Multiple Myeloma

Investigator-assessed confirmed response*

	VD (n = 60)	VTD (n = 60)	VMP (n = 62)
≥VGPR	15%	23%	24%
CR/nCR	13%	18%	15%
PR	45%	47%	27%
ORR (PR + ≥VGPR)	60%	70%	52%
Stable disease	15%	15%	27%
Progressive disease	2%	0%	6%

V = bortezomib; D = dexamethasone; T = thalidomide; M = melphalan; P = prednisone; VGPR = very good partial response; CR/nCR = complete or near-complete response; PR = partial response; ORR = overall response rate

* Response-evaluable population: Received at least one dose of study drug and at least one postbaseline M-protein measurement

Niesvizky R et al. *Proc ASH* 2009; **Abstract 129**.

Case discussion

A 53-year-old man presents with several lytic lesions and spinal cord compression and is diagnosed with ISS Stage I MM (from the practice of Dr Deutsch).

SELECTION OF INDUCTION THERAPY FOR NEWLY DIAGNOSED MM

► **DR LOVE:** David, how accurate is staging with regard to prognosis?

► **DR VESOLE:** In 2005 the International Staging System was published in the *Journal of Clinical Oncology*. However, the survival times are outdated because none of those patients received immunomodulatory drugs or a proteasome inhibitor (Greipp 2005). Also, the data set did not have enough cytogenetic and FISH information to be incorporated into the staging system.

Ultimately, the system will be revised incorporating additional cytogenetic information, and we'll probably have a modified staging system in the not-too-distant future. Nevertheless, patients who have early-stage disease fare better than those with more advanced-stage disease.

► **DR LOVE:** What treatment would you offer to this patient?

► **DR VESOLE:** My initial decision would be whether to administer radia-

2.6

International Staging System (ISS) for Multiple Myeloma

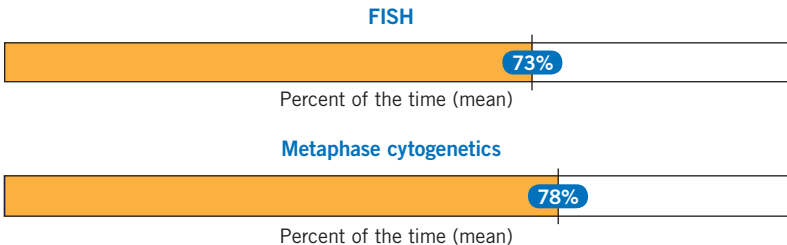
Variables contributing to ISS calculation: Serum β 2-microglobulin; albumin

Stage	ISS criteria	% of patients	Median survival
I	Serum β 2-microglobulin < 3.5 mg/dL Serum albumin \geq 3.5 g/dL	28%	62 mo
II	Neither Stage I nor Stage III	33%	44 mo
III	Serum β 2-microglobulin \geq 5.5 mg/L	39%	29 mo

Greipp PR et al. *J Clin Oncol* 2005;23(15):3412-20.

2.7

Approximately what percent of the time do you order the following tests for patients with newly diagnosed multiple myeloma?



Research To Practice. Patterns of Care Study of 100 US-Based Oncologists, October 2009.

tion therapy first or to proceed directly to laminectomy, which would depend on the degree of cord compression and neurological compromise.

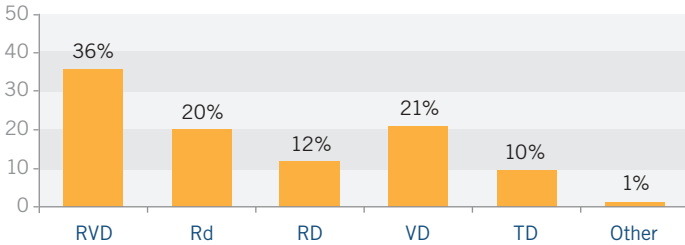
I use radiation therapy sparingly. If he had already undergone laminectomy and his spinal cord compression was relieved, then I would treat with chemotherapy and no radiation therapy. The most common triple therapy is RVD, which I would probably use for a young patient.

The data on up-front RVD have recently been submitted for publication, and they are impressive. The response rate is 100 percent, the complete response rate is approximately 40 percent and the patients who achieved very good partial response or greater is 74 percent.

The RVD regimen is potent, and for the most part it's well tolerated (2.9). A clinical trial is currently comparing RVD to lenalidomide/dexametha-

2.8

The patient underwent fusion of T10-T12 and radiation therapy to the low thoracic spine. Which, if any, additional systemic therapy other than a bisphosphonate would you recommend?



Research To Practice Satellite Symposium, December 4, 2009: Rounds with the Investigators. Results of audience polling (N = 93)

2.9

Phase I/II Study of Lenalidomide, Bortezomib and Dexamethasone (RVD) in Newly Diagnosed Multiple Myeloma: Efficacy Data

Best response to treatment overall and in the Phase II population

Response	All patients (n = 66)	Phase II (n = 35)
CR	29%	37%
nCR	11%	20%
VGPR	27%	17%
PR	33%	26%
CR + nCR	39%	57%
CR + nCR + VGPR	67%	74%
At least PR	100%	100%

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

Richardson PG et al. *Proc ASH* 2009; **Abstract 1218**.

some (SWOG-S0777), and another is comparing RVD to bortezomib/dexamethasone (ECOG-E1A05) to determine whether this triple therapy is a better approach.

► **DR STADTMAUER:** The International Staging System doesn't factor into my treatment decision for a patient such as this one. I tell my patients, "Myeloma is like pregnancy. You're either pregnant or you're not. You have myeloma."

However, I do note that this patient is relatively asymptomatic after surgery, and this does factor into my decision-making. In this case, I would use lenalidomide and dexamethasone.

When selecting the initial therapy, my decision has a lot to do with issues such as access to intravenous versus oral medications and patient preference in terms of what their interests are. We're fortunate that we have a number of active regimens to choose from. ■

SELECT PUBLICATIONS

Greipp PR et al. **International staging system for multiple myeloma.** *J Clin Oncol* 2005;23(15):3412-20.

Niesvizky R et al. **Phase 3b UPFRONT study: Interim results from a community practice-based prospective randomized trial evaluating three bortezomib-based regimens in elderly, newly diagnosed multiple myeloma patients.** *Proc ASH* 2009; **Abstract 129.**

Palumbo A et al. **Bortezomib, melphalan, prednisone and thalidomide (VMPT) followed by maintenance with bortezomib and thalidomide (VT) for initial treatment of elderly multiple myeloma patients.** *Proc ASH* 2009; **Abstract 128.**

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 randomised controlled trial.** *Lancet Oncol* 2010;11:29-37.

Richardson PG et al. **High response rates and encouraging time-to-event data with lenalidomide, bortezomib, and dexamethasone in newly diagnosed multiple myeloma: Final results of a Phase I/II study.** *Proc ASH* 2009; **Abstract 1218.**

CHRONIC MYELOID LEUKEMIA (CML)

Case discussion

A 44-year-old man presents with chronic-phase CML and imatinib 400 mg/day was initiated (from the practice of Kenneth R Hoffman, MD, MPH).

MONITORING CML WITH CYTOGENETIC AND MOLECULAR TESTING

► **DR LOVE:** Susan, would you talk about disease monitoring in patients with CML (3.1)?

► **DR O'BRIEN:** Both the NCCN guidelines and the European LeukemiaNet Guidelines are evidence based and suggest that the goal should be a

complete cytogenetic response, preferably by 12 months (Baccarani 2006).

The monitoring guidelines recommend a polymerase chain reaction (PCR) check every three months or, if the patient's disease becomes molecularly negative, shifting to

every six months. I believe one of the problems with molecular monitoring, however, is that we tell people to do it, but then we don't tell them what to do with their results.

My approach is that if it's low and it's staying low, that's fine. If it's rising, then you don't do anything based on the PCR by itself, but it may indicate that you should order another test.

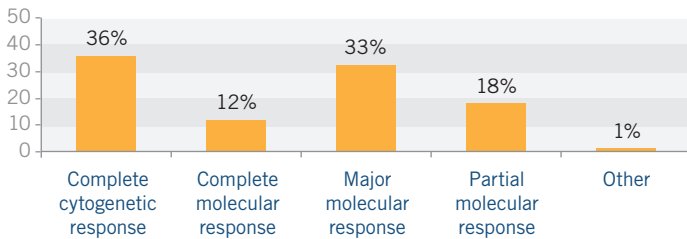
Why do we not have guidelines like those we have for cytogenetic response or hematologic response — if you don't reach this point by this time, do you change therapy? It's

because the molecular data continue to emerge and change.

In general, the guidelines state that if the PCR result increases more than a log, that should trigger cytogenetic testing. If evidence of cytogenetic relapse is present, then a mutation analysis should be conducted to discover whether the BCR-ABL is mutated (3.2). This is based on the IRIS data, for which updated results are usually presented every year at ASH (Deininger 2009; O'Brien 2008). I believe that in general we should not change therapy based on the PCR.

3.1

Inability to maintain which of the following is most representative of "imatinib failure" in a patient with CML?

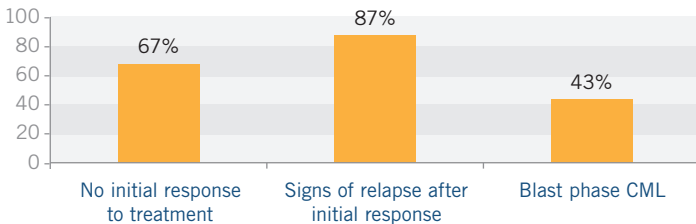


Conducted in October 2009 (n = 100 medical oncologists)

Research To Practice. Patterns of Care Study of 100 US-Based Oncologists, October 2009.

3.2

For which of the following patient types have you ordered an ABL kinase domain mutation analysis?



Conducted in October 2009 (n = 100 medical oncologists)

Research To Practice. Patterns of Care Study of 100 US-Based Oncologists, October 2009.

If the PCR is rising then other tests like cytogenetics should be performed

and therapy may be changed on the basis of alternate tests.

NILOTINIB VERSUS IMATINIB IN NEWLY DIAGNOSED CML

► **DR LOVE:** Michael, would you comment on the Phase III ENESTnd trial being reported here at the ASH 2009 meeting?

► **DR MAURO:** This three-arm trial evaluated two different doses of nilotinib versus standard imatinib for patients with newly diagnosed chronic-phase CML.

The authors reported more rapid cytogenetic and molecular responses and reduction in disease-progression events with nilotinib at the 12-month endpoint (Saglio 2009; [3.3]).

The endpoint of major molecular response at 12 months was chosen

as it is expected to translate into a survival or progression-free survival advantage. These results may be enough to hoist nilotinib onto the podium to displace imatinib as our front-line therapy preference.

► **DR O'BRIEN:** What I find compelling in these data is the transformation to accelerated or blast crisis. That's an obvious endpoint, which everyone would accept as relevant.

A significant difference was apparent — less than one percent of patients on each of the nilotinib arms and approximately four percent of patients on the imatinib arm transformed to accelerated or blast crisis.

3.3

ENESTnd: Molecular and Cytogenetic Response Rates in a Phase III Study Comparing Nilotinib to Imatinib for Patients with Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase

"846 pts with newly diagnosed Ph+ CML-CP, diagnosed within 6 mos, and stratified by Sokal risk score, were randomized 1:1:1 to nilotinib 300 mg bid (n = 282), nilotinib 400 mg bid (n = 281), and imatinib 400 mg qd (n = 283) arms. The primary endpoint was rate of major molecular response (MMR) at 12 months (mos). All pts had a minimum of 12 mos of treatment or discontinued early; median follow-up was 14 mos. MMR was defined as a value of $\leq 0.1\%$ of BCR-ABL/ABL ratio on the International Scale. Molecular response was assessed by RQ-PCR at baseline, monthly for 3 mos and every 3 mos thereafter..

Nilotinib at both 300 mg bid and 400 mg bid induced significantly higher and faster rates of MMR and CCyR compared with imatinib 400 mg qd, the current standard of care in pts with newly diagnosed CML.

Nilotinib was effective across all Sokal scores. After only one year of treatment, both nilotinib arms resulted in a meaningful clinical benefit compared to imatinib, with reduction of transformation to AP/BC.

Nilotinib exhibited a favorable safety and tolerability profile. The superior efficacy and favorable tolerability profile of nilotinib compared with imatinib suggests that nilotinib may become the standard of care in newly diagnosed CML."

MMR = major molecular response; CCyR = complete cytogenetic response; AP = accelerated phase; BC = blast crisis

Saglio G et al. *Proc ASH 2009*; **Abstract LBA-1.**

That may be the most striking result in terms of the practical effect of administering nilotinib up front. I

believe it's enough to obtain approval for nilotinib.

Case discussion

A 71-year-old woman with Crohn's disease is diagnosed with chronic-phase CML and maintains cytogenetic remission for seven years despite incomplete adherence to imatinib therapy, at which time FISH reveals 33 percent of cells positive for BCR-ABL (from the practice of Dr Schwartz).

ADHERENCE TO IMATINIB

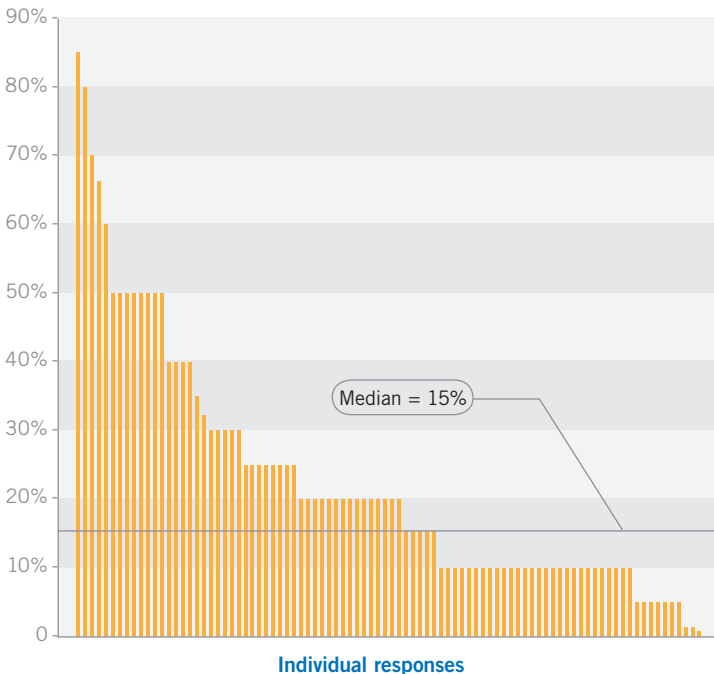
► **DR MAURO:** We know that the imatinib plasma level is a good predictor of subsequent response. In one study, patients used electronic

bottles that recorded when they took a pill. A calendar showed how patients were adherent for a while, then took a break during the holidays. Then they

3.4

Approximately what percent of your patients with CML are less than "acceptably" adherent to imatinib therapy?

(Responses from the 90 of 100 physicians who have observed patients less than acceptably adherent)



Research To Practice. Patterns of Care Study of 100 US-Based Oncologists, October 2009.

made a New Year's resolution and began taking it again. Then, a week before their appointment, they took twice the dose and the plasma level was high when drawn.

I'd hate to see a physician select a clinical intervention based on a single plasma level. As it stands now, it's not a great tool to monitor compliance, but it could be.

3.5

Association between Adherence to Imatinib and the Six-Year Probability of Major Molecular Response (MMR) or Complete Molecular Response (CMR) in Patients with CML

	Adherence ≤ 90% (n = 23)	Adherence > 90% (n = 64)	p-value
Six-year probability of MMR	28.4%	94.5%	<0.0001
Six-year probability of CMR	0%	43.8%	0.002

Multivariate analysis identified adherence and expression of the molecular transporter hOCT1 as the only independent predictors for MMR. Adherence was the sole independent predictor for CMR.

“We found a strong association between adherence rate (≤90% or >90%) and the 6-year probability of major molecular response (MMR) (28.4% vs 94.5%, $p < 0.0001$) and complete molecular response (CMR) (0% vs 43.8%, $p = 0.002$). Multivariate analysis identified adherence (RR = 11.7, $p = 0.001$) and expression of the molecular transporter hOCT1, (RR = 1.79, $p = 0.038$) as the only independent predictors for MMR. Adherence was the sole independent predictor for CMR. No molecular responses were observed when the adherence was ≤20% ($p = 0.0001$). In patients whose imatinib dose had been increased (n = 32) the adherence was poor (median 86.4%). Adherence was the only independent predictor for failure to achieve a 3-log transcript reduction (RR = 17.66, $p = 0.006$) in this subgroup of patients. Patients with CML vary greatly in their response, as demonstrated originally by Sokal et al in 1984, and the same variation is seen in patients treated with imatinib in the modern era. The basis for this variation is unknown but it has been attributed to the intrinsic biological heterogeneity of the leukemia. In contrast we show here that adherence to therapy is the major factor determining the degree of response that a CML patient treated with imatinib will achieve.”

Bazeos A et al. *Proc ASH* 2009; **Abstract 3290**.

IMATINIB DOSE ESCALATION

► **DR LOVE:** If you feel that a patient's disease is progressing on imatinib and you want to increase the dose, how high will you escalate it?

► **DR O'BRIEN:** The highest dose I've used is 800 mg. We've used high-dose imatinib a lot at MD Anderson, and if you examine our data or data from the TOPS trial, the randomized study comparing 400 to 800 mg,

you see that most patients can receive more than 400 mg. Not everyone can tolerate 800 mg, but most patients can tolerate 600 mg.

When I do escalate the dose, I increase from 400 to 800 mg and only use 600 mg if a patient can't tolerate the higher dose.

► **DR MAURO:** I too go directly to 800 mg. Data from randomized trials

comparing dose increase to switching agents after imatinib failure indicate that smaller incremental dose changes aren't as effective as doubling the dose or switching agents.

► **DR O'BRIEN:** As an aside, one of the reasons to monitor patients using the PCR is that published data show that regardless of whether your intervention is to increase the dose or switch

drugs, the outcome is better if you intervene at a cytogenetic rather than a hematologic relapse.

However, if the patient cannot be monitored well and does experience hematologic relapse, I switch to a second-generation tyrosine kinase inhibitor rather than increase the dose. ■

SELECT PUBLICATIONS

Baccarani M et al; European LeukemiaNet. **Evolving concepts in the management of chronic myeloid leukemia: Recommendations from an expert panel on behalf of the European LeukemiaNet.** *Blood* 2006;108(6):1809-20.

Bazeos A et al. **Long term adherence to imatinib therapy is the critical factor for achieving molecular responses in chronic myeloid leukemia patients.** *Proc ASH* 2009;**Abstract 3290.**

Cortes J et al. **Efficacy of nilotinib in patients (Pts) with newly diagnosed, previously untreated Philadelphia chromosome (Ph)-positive chronic myelogenous leukemia in early chronic phase (CML-CP).** *Proc ASH* 2009a;**Abstract 341.**

Cortes JE et al. **Pharmacokinetic/pharmacodynamic correlation and blood-level testing in imatinib therapy for chronic myeloid leukemia.** *Leukemia* 2009b;23(9):1537-44.

Deininger M et al. **International randomized study of interferon versus STI571 (IRIS) 8-year follow-up: Sustained survival and low risk for progression or events in patients with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) treated with imatinib.** *Proc ASH* 2009;**Abstract 1126.**

Noens L et al. **Prevalence, determinants, and outcomes of nonadherence to imatinib therapy in patients with chronic myeloid leukemia: The ADAGIO study.** *Blood* 2009;113(22):5401-11.

O'Brien SG et al. **International randomized study of interferon versus STI571 (IRIS) 7-year follow-up: Sustained survival, low rate of transformation and increased rate of major molecular response (MMR) in patients (pts) with newly diagnosed chronic myeloid leukemia in chronic phase (CMLCP) treated with imatinib (IM).** *Proc ASH* 2008;**Abstract 186.**

Pagnano K BB et al. **Impact of imatinib dose escalation in chronic myeloid leukemia patients in chronic phase with sub-optimal response or failure with imatinib 400 mg.** *Proc ASH* 2009;**Abstract 3289.**

Rosti G et al. **Nilotinib 800 mg daily as frontline therapy of Ph + chronic myeloid leukemia: Dose delivered and safety profile for the GIMEMA CML Working Party.** *Proc ASH* 2009;**Abstract 2205.**

Saglio G et al. **Nilotinib demonstrates superior efficacy compared with imatinib in patients with newly diagnosed chronic myeloid leukemia in chronic phase: Results from the international randomized phase III ENESTnd trial.** *Proc ASH* 2009;**Abstract LBA-1.**

St Charles M et al. **Predictors of treatment non-adherence in patients treated with imatinib mesylate for chronic myeloid leukemia.** *Proc ASH* 2009;**Abstract 2209.**

Wu EQ et al. **Healthcare resource utilization and costs associated with non-adherence to imatinib treatment in chronic myeloid leukemia patients.** *Curr Med Res Opin* 2010;26(1):61-9.

Rounds with the Investigators: Challenging Cases in Multiple Myeloma, Myelodysplastic Syndrome/Acute Myeloid Leukemia and Chronic Myeloid Leukemia

QUESTIONS (PLEASE CIRCLE ANSWER):

- In the AZA-001 trial, treatment with azacitidine improved median overall survival by approximately _____ compared to conventional care regimens for patients with higher-risk MDS.
 - Three months
 - Six months
 - Nine months
 - 12 months
- In the AZA-001 trial, treatment with azacitidine delayed transformation to AML by approximately _____ compared to conventional care regimens for patients with higher-risk MDS.
 - Four months
 - Six months
 - 13 months
 - 17 months
- A study by Fernandez and colleagues of anthracycline dose intensification for patients with AML reported daunorubicin at a dose of _____ to be superior to daunorubicin at a dose of _____.
 - 90 mg/m², 60 mg/m²
 - 60 mg/m², 45 mg/m²
 - 90 mg/m², 45 mg/m²
 - None of the above
- Lenalidomide is effective in treating MDS with 5q-minus syndrome.
 - True
 - False
- In the Phase III trial evaluating bortezomib/melphalan/prednisone with or without thalidomide for elderly patients with newly diagnosed MM, the rates of peripheral neuropathy were significantly reduced when bortezomib was administered once rather than twice weekly.
 - True
 - False
- In the Phase I/II study of lenalidomide/ bortezomib/dexamethasone (RVD) in newly diagnosed MM reported at ASH 2009 by Richardson and colleagues, the rate of sensory peripheral neuropathy was _____.
 - Two percent
 - Eight percent
 - 15 percent
- In the UPFRONT trial, the three bortezomib-based regimens evaluated for elderly patients with newly diagnosed MM were bortezomib/dexamethasone, bortezomib/melphalan/prednisone and _____.
 - Bortezomib/thalidomide/ dexamethasone
 - Bortezomib/lenalidomide/ dexamethasone
- In the Phase I/II study of RVD in newly diagnosed MM reported at ASH 2009 by Richardson and colleagues, _____ of patients experienced at least a partial response.
 - 60 percent
 - 70 percent
 - 80 percent
 - 100 percent
- Data from a Phase III trial comparing nilotinib to imatinib for patients with newly diagnosed CML in chronic phase demonstrated significantly higher and faster rates of major molecular response and complete molecular response among patients who received _____.
 - Nilotinib 300 mg BID
 - Nilotinib 400 mg BID
 - Imatinib 400 mg qd
 - Both a and b
- The randomized TOPS trial compared _____ to _____ of imatinib for patients with CML.
 - 400 mg, 600 mg
 - 400 mg, 800 mg

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Rounds with the Investigators: Challenging Cases in Multiple Myeloma, Myelodysplastic Syndrome/Acute Myeloid Leukemia and Chronic Myeloid Leukemia

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
Risk stratification and initiation of systemic therapy in MDS	4 3 2 1	4 3 2 1
Dosing, scheduling and administration of azacitidine in MDS	4 3 2 1	4 3 2 1
Lenalidomide in MDS with and without 5q deletion	4 3 2 1	4 3 2 1
Anthracycline dose intensification in AML	4 3 2 1	4 3 2 1
Molecular diagnostic studies in AML	4 3 2 1	4 3 2 1
Perspective on the efficacy and safety of up-front lenalidomide, bortezomib and dexamethasone (RVD) in MM	4 3 2 1	4 3 2 1
Nilotinib versus imatinib in newly diagnosed CML	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:

Will this activity help you improve patient care?

Yes No Not applicable

If no, please explain:

Did the activity meet your educational needs and expectations?

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 in MM, MDS and the myeloid leukemias, and apply this information to clinical practice..... 4 3 2 1 N/M N/A
- Identify patients with MM who may benefit from high-dose chemotherapy with stem cell transplantation, and select induction regimens that optimize initial response and long-term outcome. 4 3 2 1 N/M N/A
- Develop an algorithm for the risk-stratified induction treatment of MDS. 4 3 2 1 N/M N/A
- Compare and contrast the benefits and risks of imatinib dose escalation versus alternative tyrosine kinase inhibitor therapy for patients with CML and evidence of residual disease. 4 3 2 1 N/M N/A
- Use prognostic and predictive clinical and molecular markers to aid in treatment decision-making for MM, MDS and the myeloid leukemias. 4 3 2 1 N/M N/A
- Assess the role of maintenance or consolidation treatment approaches in the management of AML. 4 3 2 1 N/M N/A
- Recall the emerging data for novel agents and combinations that may affect the current or future treatment of relapsed MM, MDS, AML or CML..... 4 3 2 1 N/M N/A

EDUCATIONAL ASSESSMENT AND CREDIT FORM (continued)

What other practice changes will you make or consider making as a result of this activity?

What additional information or training do you need on the activity topics or other oncology-related topics?

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 editor for this educational activity

	4 = Excellent	3 = Good	2 = Adequate	1 = Suboptimal	
Faculty	Knowledge of subject matter				Effectiveness as an educator
Aristoteles Giagounidis, MD, PhD	4	3	2	1	4 3 2 1
Michael J Mauro, MD	4	3	2	1	4 3 2 1
Susan M O'Brien, MD	4	3	2	1	4 3 2 1
Gail J Roboz, MD	4	3	2	1	4 3 2 1
Edward A Stadtmayer, MD	4	3	2	1	4 3 2 1
David H Vesole, MD, PhD	4	3	2	1	4 3 2 1
Editor	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 editor for this activity:

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Name: Specialty:

Professional Designation:

- MD DO PharmD NP RN PA Other

Medical License/ME Number: Last 4 Digits of SSN (required):

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I certify my actual time spent to complete this educational activity to be _____ hour(s).

Signature: Date:

To obtain a certificate of completion and receive credit for this activity, please complete the Post-test, fill out the Educational Assessment and Credit Form and fax both to (800) 447-4310, or mail both to Research To Practice, One Biscayne Tower, 2 South Biscayne Boulevard, Suite 3600, Miami, FL 33131. You may also complete the Post-test and Educational Assessment online at CME.ResearchToPractice.com.

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Hematologic Oncology™

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