

Myeloid Malignancies: A Look to the Future

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Statement of need

The diagnostic parameters for the myeloid malignancies are complex. Many therapies are being used, and many more novel options are being tested for the various diseases. There is a need to bring issues surrounding diagnostic and treatment decisions to the forefront for physicians treating patients with these malignancies.

Goals and objectives

All North Shore–Long Island Jewish Health System CME activities are designed to lead to improved patient care and patient safety. At the conclusion of this activity, participants should be able to:

1. Define symptoms, classification, and diagnostic differences among AML, MDS, and CML
2. Discuss the pros and cons of the current standard treatment options for the myeloid malignancies
3. Recognize unusual cases within the disease categories and assess the various treatment options for them

Target audience

Hematologists, oncologists, fellows in hematology/oncology, allied health professionals

CME accreditation

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North Shore–Long Island Jewish Health System

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INTRODUCTION

This CME monograph on myeloid malignancies is an outgrowth of a meeting held in Chicago in June 2007 entitled, Myeloid and Lymphoid Malignancies: A Look to the Future. This title has a dual significance insofar as the meeting was a look to the future in 2 ways. The presenting faculty members were all oncology fellows who are outstanding representatives of their chosen fields. As such, they will become future thought leaders and opinion makers of tomorrow. The other forward-looking aspect of the meeting was the topics and ensuing discussion: they have implications for the future treatment of these diseases. The fresh perspectives provided by these keen young doctors shed new light on critical issues associated with the management of hematologic malignancies both now and in the future.

Hematologic malignancies have considerable impact on many individuals. Approximately 218,659 people in the United States are either living with leukemia or are in remission from it.¹ Approximately 44,240 new cases are diagnosed in the US each year, of which 13,410 are acute myeloid leukemia (AML) and 4,570 are chronic myeloid leukemia (CML).² In addition, 14,000 people are diagnosed each year with myelodysplastic syndromes.² 9,480 Americans will have died from AML and CML in 2007.²

The lymphoid and myeloid malignancies are quite distinct, as the case studies in each monograph will demonstrate, and vary significantly in their causes and natural progression. The oncology fellows who presented these cases work with prominent hematologists at major medical or cancer centers. Their mentors critiqued these presentations in person at the meeting and in manuscript form prior to publication. Their guidance and influence have been crucial to the development of these young doctors. The mentors are: Martin S. Tallman, MD, Northwestern University Feinberg School of Medicine; Dan Douer, MD, University of Southern California; and Richard Silver, MD, Weill Medical College of Cornell University.

The cases were chosen to be instructive, either because they were typical presentations of the disease or they presented particular issues that required special consideration. The case studies on the myeloid malignancies – acute myeloid leukemia, myelodysplastic syndromes, and chronic myeloid leukemia – are presented here. The lymphoid malignancies are covered in a companion monograph.

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CASE 1. ACUTE MYELOID LEUKEMIA, INCLUDING PROMYELOCYTIC LEUKEMIA

Jessica Altman, MD; Martin Tallman, MD

Background

Acute promyelocytic leukemia (APL) is a subtype of acute myelogenous leukemia (AML). It is also known as acute promyelocytic leukemia. APL comprises 10%–15% of adults with AML. The median age of patients with APL is 30–40 years, although it is seen in all age groups. APL is characterized by the balanced reciprocal chromosomal translocation t(15;17) and the creation of the fusion gene product *PML/RAR* alpha. Standard treatment for APL includes anthracycline-based chemotherapy in combination with all-trans retinoic acid (ATRA).

Case History

The patient is a 47-year-old man who presented to his primary care physician for follow-up of chronic medical problems. A routine complete blood count (CBC) revealed a white blood cell count (WBC) of 1,500/ μ L, hemoglobin of 10 g/dL, and platelets of 75,000/ μ L.

Two weeks later, a repeat CBC showed a WBC of 1,000/ μ L, and he was referred to a hematologist. He was promptly transferred to Northwestern University Medical Center for further evaluation and care. He had a past medical history significant for ischemic cardiomyopathy with a left ventricular ejection fraction (LVEF) of 25% with an implantable cardioverter-defibrillator, diabetes mellitus, and obstructive sleep apnea syndrome.

His examination was notable for distant heart tones, no organomegaly, and no petechiae. Pertinent laboratory studies during the time of the initial evaluation at Northwestern were: WBC 800/ μ L (52% neutrophils, 3% eosinophils, 33% lymphocytes, 4% myelocytes, 4% promyelocytes, 4% basophils, and 2% nucleated red blood cells), hemoglobin 10.6 g/dL, platelets 65,000/ μ L, prothrombin time (PT) 17.2 seconds, partial thromboplastin time (PTT) 30.1 seconds, fibrinogen 171 mg/dL, D-dimer >4 ng/mL. His kidney and liver function tests were normal.

Bone marrow biopsy was morphologically consistent with APL. Flow cytometry revealed a population expressing CD13+, CD33+, (myeloperoxidase) MPO+ cells. These cells had very dim CD45+ staining, dim CD34+ and CD117+ staining, and very dim human leukocyte antigen DR-1 (HLADR) + to HLADR- staining. RT-PCR was positive for *PML/RAR*-alpha fusion transcript.

Treatment

Due to his profound cardiomyopathy, the decision was made to treat the patient with arsenic trioxide (ATO) and all-trans retinoic acid (ATRA) in lieu of standard therapy with anthracycline chemotherapy and ATRA. On day 6 of treatment, his WBC increased from 7,000/ μ L to 16,000/ μ L with 82% promyelocytes. He developed the APL differentiation syndrome, which rapidly improved with steroids. His percent promyelocytes declined immediately. After he completed his first cycle of 5 weeks of therapy, his bone marrow was morphologically free of disease and RT-PCR for *PML/RAR* alpha was negative. He completed 3 of 4 planned cycles of ATRA/ATO, but the fourth cycle was cancelled due to peripheral neuropathy. The patient is currently receiving maintenance therapy with ATRA/6-mercaptopurine/methotrexate and his molecular studies continue to be negative. A summary of the patient's characteristics and treatment can be found in Table 1.

Table 1. Clinical features of an adult male with acute promyelocytic leukemia

Age (yrs)	WBC (μ L)	Hemoglobin (g/dL)	Plts (μ L)	Flow cytometry									TX	Clinical outcome
				CD 13	CD 33	CD 34	CD 45	CD 117	MPO	HLA DR	<i>PML-RAR</i> alpha			
47	800	10.6	65,000	+	+	dim +	dim +	dim +	+	dim + to-	+	ATO and ATRA 3 of 4 planned cycles	Maintenance therapy of ATRA/6-mercaptopurine/methotrexate	

ATO, arsenic trioxide; ATRA, all-trans retinoic acid; HLADR, human leukocyte antigen DR-1; tx, treatment; WBC, white blood cell count; yrs, years

Discussion

This case was selected to highlight some important concepts and recent advances in the treatment of APL. The current standard of care for newly diagnosed APL includes induction and consolidation with ATRA and anthracycline-based chemotherapy and maintenance with low-dose chemotherapy and ATRA.³⁻⁵ The role of maintenance therapy has recently been questioned in patients who are molecularly negative after intensive consolidation chemotherapy. The study by the Japan Adult Leukemia Study Group found no benefit to

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intensive maintenance chemotherapy in this setting.⁶ The GIMEMA Italian cooperative group tested the benefits of either ATRA, low-dose chemotherapy with methotrexate and 6-mercaptopurine, or the combination of ATRA and the same low-dose chemotherapy and found no benefit to maintenance therapy in molecularly negative patients.⁷

Most patients with relapsed APL are treated with ATO, which induces high complete remission (CR) rates. Prompted by initial studies from China, a US multicenter trial of ATO in patients with relapsed or refractory APL showed a CR rate of 85%, a molecular remission rate of 86%, and an overall survival (OS) of 77% at 2 years.⁸ Other trials have demonstrated similar high CR rates.⁹⁻¹² ATO appears to be the most effective single agent in APL due to its ability to induce molecular CR in the great majority of patients after one or two 25-day cycles.

In the recent North American Intergroup trial C9710, patients randomized to 2 courses of ATO as an early consolidation fared better than those who did not receive ATO.¹³ Favorable results in high-risk patients have also been reported among those receiving higher doses of idarubicin and either high- or intermediate-dose ara-C in induction or consolidation.¹⁴⁻¹⁶ These trials have encouraged the study of ATO in patients with newly diagnosed APL.

In a randomized prospective trial, Shen and colleagues treated 61 newly diagnosed APL patients with either ATO (0.16 mg/kg/d), ATRA (15 mg/m²/d), or the combination of ATO and ATRA.¹⁷ The CR rates in the 3 groups were similar (>90%). The patients treated with the combination of ATO and ATRA achieved a shorter time to CR (25.5 days compared to 40.5 for ATRA and 31 for ATO), faster platelet recovery, and greater reduction in *PML/RAR*-alpha fusion gene. Of the 20 patients in the combination group, 100% remained in CR at a median of 18 months compared to 26% of patients relapsing in the ATRA group in 13 months, and 11% relapsing in the ATO group at 12 months.

Estey and colleagues studied ATRA plus ATO therapy for

both induction and post remission therapy in 49 patients (45 mg/m² ATRA and 0.15 mg/kg), adding gemtuzumab ozogamicin (GO) for high-risk patients (defined by high WBC, PCR positivity). CR rates were 89% (39 of 44) at 28 days.¹⁸

Given this patient's cardiomyopathy and his low-risk disease, our goal was to minimize exposure to anthracyclines. Therefore, the combination of ATRA and ATO was chosen given the encouraging data from Shen, Estey, and others. During induction, the patient developed symptoms of APL differentiation syndrome, and he improved quickly with steroids. His therapy was not held, and he did not require treatment with GO or an anthracycline.

Summary

The current standard for induction therapy for patients with untreated APL remains anthracycline-based chemotherapy in combination with ATRA. Our suggestions for the study of ATO in untreated APL occur predominantly in the context of a clinical trial and those instances where patients may be unable to receive or tolerate anthracycline chemotherapy, including cardiac failure, secondary APL (with prior anthracycline exposure and maximum suggested exposure), and refusal of chemotherapy (Jehovah's Witness or the elderly with poor performance status). In these circumstances, treatment with ATO in combination with ATRA can be considered. Recent data suggest that some patients with very low-risk disease may do well with arsenic alone.¹⁹ Our curative goal in the treatment of APL is summarized in Table 2.

Table 2: Guidelines for curative strategies in acute promyelocytic leukemia

Situation	Recommended Strategy
Diagnosis suspected	Initiate treatment with ATRA without waiting for genetic confirmation
Coagulopathy present	Transfuse platelets to maintain the platelet count above 30,000-50,000/uL and transfuse cryoprecipitate to maintain the fibrinogen level >100-150 mg/dL
Induction therapy	Anthracycline-based chemotherapy with ATRA. ATRA + ATO if unable to tolerate anthracyclines.
Consolidation therapy	Anthracycline-based chemo + ATRA for 2 cycles to molecular negativity.
High-risk patients (those presenting white blood cell count of 10,000/uL or higher)	The strategies of higher doses of idarubicin and high- or intermediate-dose ara-C in induction or consolidation or ATO in consolidation appear effective. Intrathecal therapy can be considered for high-risk patients
Maintenance	Consider either ATRA or ATRA plus low-dose chemotherapy with 6-MP and methotrexate.
Molecular monitoring	Check RT-PCR for the <i>PML/RAR</i> alpha from the peripheral blood every 3-6 months. High-risk patients should be monitored more frequently than low- and intermediate-risk patients.
Relapse	ATO for 2 cycles until achievement of molecular remission followed by high-dose chemotherapy and autologous hematopoietic stem cell transplantation. Consider prophylactic intrathecal therapy for any patient who has a relapse. ⁴⁵ Consider allogeneic stem cell transplantation for those patients who remain PCR positive.

6-MP, 6-mercaptopurine; ATO, arsenic trioxide; ATRA, all-trans retinoic acid; RT-PCR, reverse transcriptase-polymerase chain reaction

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CASE 2. MYELODYSPLASTIC SYNDROMES

Warren Banta, MD; Dan Douer, MD

Background

Myelodysplastic syndromes (MDS) belong to a heterogeneous group of clonal hematopoietic stem cell disorders characterized by ineffective hematopoiesis, progressive cytopenias, morphologic abnormalities, and propensity to transform to AML. It is the most common hematologic malignancy in the elderly, and the incidence of the disease increases with age. The annual incidence in the US is 14,000 cases. The disease has significant morbidity, mortality, and healthcare costs.

Case History

The patient is an 80-year-old Caucasian woman who initially presented to her primary physician in 1995 for some slight abnormalities in her blood counts. Her white blood cell count (WBC) was 3300/ μ L with a normal differential and normal hemoglobin count and platelet count of 47,000/ μ L. Follow-up examinations that were done over the next few years showed similar results.

A bone marrow examination done in March 2004 showed hypocellularity of 20%–40%, with a slight maturation arrest and a relative myeloid hypoplasia and <10% blasts. Flow cytometry showed <10% of cells were CD33+, CD34+, CD13+, CD117+, and HLA-DR+. The chromosome analysis was normal female, 46 XX. The bone marrow was consistent with MDS of FAB subtype of refractory anemia (RA) with excess of blasts. In patients with less than 5% blasts, the WHO classification distinguishes between RA and refractory cytopenia with multilineage dysplasia (RCMD).²⁰ Patients with 5%–20% blasts in the bone marrow are characterized as having refractory anemia with excess blasts. The WHO classification was validated by showing that patients with RA have a better prognosis than those with RCMD.²¹

The patient presented to Norris Cancer Center/USC Medical Center in April 2005 for evaluation of pancytopenia and MDS. The patient's review of symptoms and physical exam were essentially unremarkable. The patient was generally in good health with excellent performance status. The blood count showed a WBC of 3000/ μ L, with a differential of 50% neutrophils, 46% lymphocytes, 1.7% monocytes, and 1.4% eosinophils; hemoglobin 13.4 g/dL, hemat-

ocrit 38.9 SI units, mean corpuscular volume 111 fL, and a platelet count of 63,000/ μ L.

Based on this complete blood count (CBC) and bone marrow results, the patient was determined to have myelodysplastic syndrome with an International Prognostic Scoring System (IPSS) group of Intermediate 1 (Table 3). The IPSS is based on the number of blasts in the bone marrow, the chromosomal results of the bone marrow, and the number of lineages affected. Intermediate-1 patients have a median survival of 3.5 years.²² Anemia is the most common clinical problem in low- to intermediate-1-risk MDS. Her blood counts were followed, but no treatment was initiated at that time.

Table 3. Clinical features at diagnosis of an adult female with myelodysplastic syndrome

Age (yrs)	WBC (/ μ L)	Platelets (/ μ L)	HGB (g/dL)	ANC (/ μ L)	IPSS	BM examination	Tx	Outcome
78	3000	63,000	13.4	-	Int-1	Consistent with Int-1	None at this time	Worsening cytopenias over 1 year

ANC, absolute neutrophil count; BM, bone marrow; HGB, hemoglobin; int, intermediate; IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndromes; RBC, red blood cell; tx, treatment; WBC, white blood cell count

Treatment

In March 2006, about 1 year after the initial consult, her CBC showed worsening cytopenias of all cell lines. The patient was then followed more frequently and was started on erythropoietin and pegfilgrastim (Neulasta®) with a good response in her counts. Treatment with erythropoietin improves the hemoglobin level and has an expected response rate of 20%.²³ Adding very small doses of G-CSF to erythropoietin can improve the erythropoietic response to 40%–50%.^{23,24}

In August 2006, the patient's WBC was 1700/ μ L with an absolute neutrophil count (ANC) of 900/ μ L, hemoglobin of 7.9 g/dL, and platelet count of 40,000/ μ L (Table 4, page 6). The patient then became red blood cell (RBC) transfusion-dependent despite maximal doses of erythropoietin, requiring RBC transfusion once a week. In December 2006 her serum ferritin was 2500 ng/mL and desferoxamine was prescribed to prevent iron overload.

In January 2007 a bone marrow examination revealed a hypercellular marrow (90%) with moderate dysplasia, and <3% blasts consistent with MDS (refractory anemia). Cytogenetic examination was reported as normal. Given the worsening thrombocytopenia and increased frequency of red blood cell transfusion and the need for platelet transfusions, it was decided to try to treat the underlying MDS in an attempt to reduce and possibly eliminate the need

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Table 4. Clinical features of an adult female with myelodysplastic syndrome after treatment with erythropoietin and pegfilgrastim

Age (yrs)	WBC (/μL)	Platelets (/μL)	HGB (g/dL)	ANC (/μL)	IPSS	BM examination	Tx	Outcome
79	1700	40,000	7.9	900	Int-1	90% hypercellular marrow, moderate dysplasia, and <3% blasts consistent with MDS (refractory anemia)	erythropoietin and pegfilgrastim	Worsening thrombocytopenia including RBC transfusion

ANC, absolute neutrophil count; BM, bone marrow; HGB, hemoglobin; int, intermediate; IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndromes; RBC, red blood cell; tx, treatment; WBC, white blood cell count

for transfusions. The goal of the treatment would be a hematologic improvement (HI), even if a complete remission could not be achieved. The options that were discussed with the patient were intensive chemotherapy, low-intensity treatment using FDA-approved drugs for MDS, or a clinical trial. Intensive chemotherapy was not recommended because of her age and high risk of treatment. The patient later opted for a clinical trial.

In February 2007, the patient received tipifarnib (Zarnestra®) 300 mg orally twice daily on days 1-21 and low dose ara-C 15 mg/m² subcutaneously twice daily on days 1-10. On day 20, the patient received a blood and platelet transfusion and then did not require further transfusions. After 1 cycle of treatment, her blood counts clearly showed response by increasing platelet and RBC counts. She received another cycle of tipifarnib and low dose ara-C early in March. Later that month, her WBC was 3100/μL with normal differential and ANC of 2300/μL, hemoglobin of 11.7 g/dL, and platelet count of 83,000/μL.

The patient continued with additional cycles of the same doses of tipifarnib and low-dose ara-C after the bone marrow showed complete response (Table 5). In May 2007, a bone marrow biopsy showed mild hypercellularity (50%) with trilineage maturation, mild dysplasia, and blasts <2%. Cytogenetic examination was

Table 5. Clinical features of an adult female with myelodysplastic syndrome after treatment with tipifarnib and low-dose ara-C

Age (yrs)	WBC (/μL)	Platelets (/μL)	HGB (g/dL)	ANC (/μL)	IPSS	BM examination	Tx	Outcome
80	3100	83,000	11.7	2300	Int-1	50% hypercellularity with trilineage maturation, mild dysplasia and <2% blasts	Combination of tipifarnib at 300mg and low dose ara-C at 15 mg/m ²	Complete response

ANC, absolute neutrophil count; BM, bone marrow; HGB, hemoglobin; int, intermediate; IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndromes; RBC, red blood cell; tx, treatment; WBC, white blood cell count

normal. According to the protocol, the patient can receive up to 12 cycles of the combination.

Discussion

Three drugs are now approved by the FDA for the treatment of MDS. All 3 can be myelo-suppressive, and one has to consider worsening of neutropenia and thrombocy-

topenia as side effects, which increase the risks for infections and bleeding complications. The patients can be treated with 1 of the 3 drugs and have a 25%-30% chance of a major hematologic improvement and becoming transfusion independent. A short summary of each drug can be found in Table 6 (page 7).

The first drug is azacytidine, which is a demethylating agent. The Cancer and Leukemia Group B (CALGB) performed a randomized trial in all subtypes of MDS at a dose of 75 mg/m² subcutaneously for 7 days per cycle compared to supportive care.^{25,26} The hematologic improvement rate was 37% with a complete remission (CR) rate of 7% and partial remission (PR) of 16%; 45% became transfusion independent. Azacytidine did not increase survival compared to supportive care.

Decitabine is another demethylating agent that was studied in two phase 2 European trials and one phase 3 American trial.²⁷⁻³⁰ In these studies, the drug was given intravenously at 15 mg/m² every 8 hours for 3 consecutive days per cycle. The hematologic improvement rate in all 3 studies was approximately 15% with 20% of patients achieving PR or CR. In the randomized trial, patients with intermediate-2 or high-risk MDS had a longer survival than those receiving supportive care. Decitabine could also

be given in another much more convenient schedule (and a total lower dose) of 20 mg/m² intravenously over 5 days, which was reported to produce a CR rate of 41%.³¹

The third drug is lenalidomide, which is a thalidomide analogue that is given orally. Lenalidomide is approved for the treatment of MDS with

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Table 6. Comparison of 3 FDA-approved drugs for treatment of MDS

Drug Name	Azacitidine	Decitabine	Lenalidomide
Type of drug	Demethylating agent (subcutaneous)	Demethylating agent (intravenous)	Thalidomide analogue (Oral)
Response rate (RR)	HI 37% CR 7% PR 16%	15%-20% achieve PR or CR; Lower dose over 5 days = 41% CR	With del(5q) 60% RR; Without del(5q) 25-30% RR
Drug vs Supportive care	Did not increase survival compared to supportive care	Intermediate-2 or high-risk show longer survival than those receiving supportive care	?

CR, complete response; HI, hematologic improvement; PR, partial response; RR, relative response

chromosomal aberrations that include del(5q), and patients treated with lenalidomide respond at rates of more than 60%.³² In patients with MDS who do not have del(5q), the drug has less activity, with 25%-30% of patients becoming transfusion independent.³³ The drug has mostly been studied in MDS patients with low- or intermediate-risk disease and improves the red blood cell count.

Summary

In order to try to improve the response rate of MDS, new drugs are being investigated either as single agents or in combination. In this case the patient was given the option to enroll on a clinical trial using subcutaneous low-dose ara-C in combination with the farnesyltransferase inhibitor tipifarnib. Early studies have shown that low-dose ara-C (usually 10 mg/m² twice a day for 10-14 days) can induce a CR rate of 15%-20% in MDS patients, but, in comparison to supportive care, this did not improve the survival rate.³⁴ Single-agent tipifarnib was shown in a small phase 2 study to produce very few CRs.³⁵ This patient received both drugs and achieved a CR. The study is still ongoing and the overall results are still yet unknown. This case demonstrates the developing hematologic problems of MDS without increase in the bone marrow blasts and no transformation to AML.

CASE 3. CHRONIC MYELOID LEUKEMIA

Benjamin Levy, MD; Richard Silver, MD

Background

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder characterized by a translocation that occurs between chromosomes 9 and 22. This translocation results in the fusion of the *BCR* and *ABL* genes, which leads to the expression of a protein with constitutive increased tyrosine kinase activity.³⁶ CML is one of the most extensively studied neoplasms, and recent advances,

including the introduction of imatinib, have caused a rapid change in the management of patients with this disorder.

CML accounts for 15% of adult leukemias. Approximately 4500 cases are diagnosed each year in the US, with a mean age at diagnosis of 67 years.

There are classically 3 phases (chronic phase, accelerated phase, and blast phase) of disease progression recognized in CML, but nearly 90% of patients diagnosed are in the chronic phase.³⁷ Most patients diagnosed with chronic phase CML are asymptomatic at presentation and are often diagnosed only after routine blood tests are performed for other reasons. When symptoms occur, as commonly seen in accelerated phase or blast phase, they typically consist of malaise, weight loss, and abdominal discomfort secondary to splenomegaly.

Case History

The patient is a 43-year-old male with no significant past medical history who presented for a routine check-up with his primary care physician. At that time he had no significant complaints. His past medical history was unremarkable, and he was not on any medications. No significant family history was noted. He has 2 healthy brothers, ages 40 and 50 years, and 1 sister, age 46 years, who is also healthy.

Clinical presentation included no complaints of any fatigue, no shortness of breath, no abdominal fullness, and he had no noted petechiae or rashes. Physical exam revealed a pleasant male in no apparent distress. He had normal conjunctivae, no hepatosplenomegaly, and no purpura.

His lab values were significant for a WBC of 180,000/ μ L and a differential that revealed 44% neutrophils, 35% lymphocytes, 2% basophils, 8% eosinophils, 10% myelocytes, and 1% promyelocytes. His smear was reviewed and showed an increased WBC with an increase in eosinophils, basophils, and myelocytes; full myeloid maturation; and an increase in platelet count. His chemistries were all normal. Upon seeing these labs, the patient's primary care physician referred the patient to New York Hospital-Cornell Medical Center for further diagnosis and management.

At New York Hospital-Cornell Medical Center, the initial comprehensive history and physical were confirmed. A bone marrow

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aspirate and biopsy were performed. The bone marrow aspirate revealed full myeloid maturation, marked granulocytic hyperplasia, megakaryocytic hyperplasia, and an increased number of eosinophils and basophils. The biopsy was noted to be hypercellular with an increased myeloid to erythroid precursor (M:E) ratio and a normal immunophenotype. Bone marrow cytogenetics revealed 90% Philadelphia chromosome positive metaphases with a 9;22 translocation. His peripheral blood PCR was positive for *BCR-ABL* fusion gene and negative for *JAK2*.

Treatment

The patient was diagnosed with CML and subsequently placed on imatinib 400 mg/day. The patient tolerated therapy well and still remains on the dose of 400 mg/day. He achieved a hematologic response after 2 months of therapy and, after 5 months, has achieved a complete cytogenetic response. The patient has also had a 2 log reduction in his qualitative PCR while on therapy. A summary of the patient's characteristics and treatment can be found in Table 7.

Table 7. Clinical features at diagnosis of an adult male with chronic myeloid leukemia

Age (yrs)	BM aspirate	BM biopsy	BM cytogenetics	Peripheral blood PCR	Treatment	Outcome
43	Full myeloid maturation, marked granulocytic hyperplasia, megakaryocytic hyperplasia, increased number of eosinophils and basophils	Hypercellular with increased M:E ratio, normal immunophenotype	90% Philadelphia positive metaphases with a 9;22 translocation	<i>BCR-ABL</i> + <i>JAK2</i> -	Imatinib 400 mg/day	Hematologic response after 2 months; complete cytogenetic response after 5 months

BM, bone marrow; M:E, myeloid to erythroid precursor; PCR, polymerase chain reaction

Discussion

CML is identified by several characteristic laboratory findings and pathologic features. Laboratory findings include a leukocytosis with a left shift, basophilia, and eosinophilia, as was seen in our patient. The leukocyte alkaline phosphatase activity is reduced and a marked elevation of serum B12 can be seen, the latter reflecting increased granulocyte burden. The bone marrow of patients with CML is usually hypercellular, and all stages of myeloid maturation are present. There is usually a predominance of myelocytes seen in the bone marrow. Megakaryocytes may be increased and Gaucher-like cells can be present in 10% of patients.³⁷ While these laboratory findings were traditionally the cornerstone of diagnosing the disease, recent targeted molecular therapy has made it imperative to make a diagnosis based on cytogenetic and molecular criteria. Thus, the gold standard for diagnosing CML includes demonstrat-

ing the presence of the Philadelphia chromosome (9;22) by cytogenetic techniques or by demonstrating the product of the 9;22 translocation, namely the *BCR-ABL* protein or the *BCR-ABL* fusion mRNA.

In the past, treatment options for CML were limited and included cytotoxic drugs such as busulfan, hydroxyurea, interferon, and allogeneic stem cell transplantation. However, in the past few years the treatment of CML has remarkably improved with the introduction of imatinib (Gleevec®).³⁸ Imatinib mesylate is a selective tyrosine kinase inhibitor of ABL, c-Kit, and PDGF-receptor and causes growth arrest in cells that express *BCR-ABL* without affecting normal cells.³⁹ Extremely favorable results observed in phase 1 and 2 trials culminated in the phase 3 IRIS trial. In this trial, imatinib was compared to IFN-alpha and cytarabine in chronic phase patients, and it demonstrated a 95% complete hematologic response and an 85% major cytogenetic response. Major molecular response and progression-free survival were also found to be superior with imatinib.⁴⁰ Based on these results and its limited side effect profile, imatinib has become the standard of care for patients in chronic phase CML.

The goal of therapy for patients started on imatinib is to achieve complete remission. This is monitored by hematologic, cytogenetic, and molecular parameters. Patients in chronic phase are started on 400 mg/day of imatinib and maintained if the following parameters are achieved: a complete

hematological response after 3 months; a cytogenetic response after 6 months; and a major cytogenetic response (Philadelphia chromosome-positive cells reduced by <35%) after 12 months, or a complete cytogenetic response after 18 months.⁴¹ In addition, molecular monitoring with qualitative PCR should be conducted every 3 to 6 months in patients who achieve a complete cytogenetic response. Qualitative PCR has emerged as a prognostic indicator, as recent studies have shown that a greater than 3 log reduction while on imatinib confers a better prognosis.⁴²

A subset of patients with CML will exhibit either primary or secondary resistance to imatinib. Primary resistance refers to patients who never respond to the imatinib, whereas secondary resistance refers to patients who have an initial response but eventually relapse, losing either hematologic or cytogenetic response.

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Resistance may develop through several mechanisms, the most common of which is reactivation of BCR-ABL kinase activity by either point mutations or gene amplification.⁴³ A mutation that has generated considerable interest recently is the T351I mutation. This mutation has been refractory not only to imatinib, but also to the new ABL-tyrosine kinase inhibitors, dasatinib and nilotinib.

For patients who are resistant to imatinib, new ABL-tyrosine kinase inhibitors have been recently developed that have proven effective in clinical trials.⁴⁴ Dasatinib is a dual ABL/SRC inhibitor that has 100- to 300-fold higher potency against *BCR-ABL* when compared with imatinib.³⁷ Dasatinib has been proven effective in both phase 1 and phase 2 trials, and it has recently been approved by the FDA for the treatment of adults with chronic phase, accelerated phase, or blast phase CML with resistance to prior therapy, including imatinib.

A selective BCR-ABL inhibitor, nilotinib, has been developed in addition to dasatinib. Nilotinib binds only to the inactive conformation of BCR-ABL, but it does not inhibit SRC kinases like dasatinib. Nilotinib shows a 20- to 50-fold greater potency than imatinib, and more importantly, it illustrates activity against most imatinib-resistant mutations, except the T351I mutation. While much of the data is preliminary, nilotinib has shown encouraging results in both phase 1 and 2 trials.

Summary

The development of new treatments for CML has dramatically changed the therapy for this disease. These targeted treatments have been derived from a better understanding of the underlying pathophysiology of CML. With the clinical introduction of imatinib in 2002 and, more recently, dasatinib and nilotinib, clinicians have witnessed unprecedented efficacy with generally well-tolerated side effects. While the success of these agents has been promising, resistance still represents a significant clinical problem. These problems are currently being investigated, and with new developments, will hopefully be overcome in the future.

Conclusion

As is the case with the lymphoid malignancies, the myeloid malignancies also present diagnostic and treatment issues that are not at all clear-cut. In APL, for example, the role of maintenance therapy in molecularly negative patients who have received intensive consolidation remains a topic of discussion, with evidence to support both sides. Other intricacies of patient treatment and management are highlighted in these cases. They include instances where patients may be unable to receive or tolerate the standard therapy. The patient with MDS demonstrates the development of hematologic problems even without transformation to AML or increasing blasts. And the discussion of CML highlights the importance of cytogenetic and molecular criteria for diagnosis as well as a discussion of resistance to imatinib. While the diseases may be classified together as myeloid malignancies, the intricacies involved in their diagnosis, treatment, and management not only vary widely from disease to disease, but from patient to patient.

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