

Lymphoid Malignancies: A Look to the Future

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Statement of need

The diagnostic and treatment parameters for the lymphoid 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 ALL, CLL, NHL, Hodgkin's lymphoma, and multiple myeloma
2. Discuss the pros and cons of the current standard treatment options for the lymphoid 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

North Shore-Long Island Jewish (LIJ) Health System is accredited by the Accreditation Council for Continuing Medical Education to provide Continuing Medical Education for physicians.

The North Shore-Long Island Jewish Health System designates this educational activity for a maximum of 1.5 *AMA PRA Category 1 Credits*™. Each physician should only claim credit commensurate with the extent of their participation in the activity.



North Shore-Long Island Jewish Health System

An educational grant from Cephalon Oncology made this activity possible.



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North Shore-LIJ for fair balance and scientific objectivity and to ensure appropriateness of patient care recommendations.

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Disclosure: No relevant financial relationship with commercial interest

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Disclosure: Consultant: Therakos; Gloucester Pharmaceuticals

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Disclosure: No relevant financial relationship with commercial interest

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Disclosure: No relevant financial relationship with commercial interest

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Lymphoid Malignancies: A Look to the Future

INTRODUCTION

This CME monograph on lymphoid 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 700,000 people in the United States are living with leukemia, lymphoma, myeloma, and other blood cancers. Over 135,000 new cases are diagnosed each year,^{1,2} and an estimated 52,300 Americans will have died from them 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: Kanti Rai, MD, Long Island Jewish Medical Center; Richard Larson, MD, University of Chicago; Guido Tricot, MD, University of Arkansas; Francine Foss, MD, Yale University Comprehensive Cancer Center; and Anas Younes, MD, MD Anderson Cancer Center.

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 lymphoid malignancies – chronic lymphocytic leukemia (CLL), acute lymphocytic leukemia (ALL), multiple myeloma, non-Hodgkin's lymphoma (NHL), and Hodgkin's lymphoma – are presented here. The myeloid malignancies are covered in a companion monograph.

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CASE 1. CHRONIC LYMPHOCYTIC LEUKEMIA

Matthew Kaufman, MD; Kanti Rai, MD, CHAIR

Background

Chronic lymphocytic leukemia (CLL), caused by an abnormal accumulation of B lymphocytes, is the most common form of leukemia in adults. Age is the key risk factor for CLL, as over 75% of new cases are diagnosed in patients over age 50. CLL occurs in men twice as often as in women. CLL usually progresses slowly, and early stage CLL is generally not treated because therapy does not improve survival time or quality of life. When a patient's quality of life begins to deteriorate, treatment is started, with the aim of controlling the disease and symptoms, rather than attempting to cure it. Common treatment includes chemotherapy, radiation therapy, biological therapy, bone marrow transplantation, splenectomy, and radiation therapy.

Case history

The patient is a 56-year-old man who was diagnosed with CLL in 2000, at the age of 49 (Table 1A). A routine complete blood count

Table 1. Clinical features of an adult male with CLL

A. At time of diagnosis

Age (years)	WBC (μL)	Small lymphocyte infiltration (%)	BM blasts (%)	Systemic Symptoms	Rai stage	CD5	CD19	CD23
49	14,000	80	90	No	0	+	+	+

BM, bone marrow; WBC, white blood count

B. At time of referral to Long Island Jewish Medical Center

Age (years)	WBC (μL)	Lymphocyte count (μL)	ANC (μL)	HGB (g/dL)	Platelets (μL)	Systemic Symptoms	ZAP-70	CD38	Immunoglobulin heavy-chain
52	130,000	120,000	5000	13	180,000	Palpable nodes in axillae and inguinal areas, palpable spleen tip	+	+	mutated

ANC, absolute neutrophil count; HGB, hemoglobin; WBC, white blood count

(CBC) in his primary care physician's office showed lymphocytosis. He was referred to a hematologist, who performed a bone marrow biopsy and peripheral flow cytometry. Both demonstrated typical flow patterns for CLL with CD19, CD5, and CD23 positivity. The bone marrow was hypercellular at 90%, with 80% infiltration of small lymphocytes. At the time of diagnosis, the patient was Rai stage 0. He did not experience any systemic symptoms, and physical exam demonstrated no evidence of disease.

Over the course of the next 3 years, his lymphocyte count increased from 14,000/μL to approximately 120,000/μL. This represented a doubling time of approximately 12 months. The rest of his CBC was normal. Fluorescence in situ hybridization (FISH) and banding revealed no cytogenetic abnormalities. However, the increase in his lymphocyte count aroused concern about when to start chemotherapy.

The patient was referred to our office at Long Island Jewish Medical Center for a second opinion (Table 1B). At this first visit to our office in 2003, he was still free of symptoms; on physical exam he appeared healthy and robust and reported being very active and feeling good. He had some small palpable nodes in the axillae and inguinal areas, and the spleen tip was just palpable. A CBC revealed a white blood cell count of 130,000/μL with a lymphocyte count of 120,000/μL. Absolute neutrophil count (ANC) was 5000/μL, hemoglobin (Hgb) was 13 g/dL, and platelets were 180,000/μL. FISH testing still showed no abnormalities. However, he tested positive for ZAP-70 and CD38, both of which are poor prognostic markers, and he had a mutated immunoglobulin heavy-chain gene, which confers a good prognosis.

Based on the patient's doubling time, prognostic markers, and symptoms, we recommended continued observation. The patient's white blood cell count (WBC) was above 100,000/μL, at which point many physicians begin treatment, especially with a doubling time of 12 months. However, the patient exhibited discordant prognostic markers. Most importantly, he was symptom-free and appeared healthy. Lymphocyte count alone should not dictate treatment, though treatment typically begins when the WBC reaches 250,000/μL, out of concern for hyperviscosity. Likewise, prognostic factors alone should not dictate a treatment plan. This is especially true

when discordant markers are present.

Two years later, the patient returned with moderate systemic symptoms (Table 1C). History revealed fatigue

with exertion, moderate weight loss of about 10 pounds, and night sweats every second night. On physical exam, the patient appeared

Table 1. Clinical features of an adult male with CLL (cont.)

C. At time of follow-up visit

Age (years)	Lymphocyte count (μL)	HGB	Platelets	Systemic Symptoms
54	160,000	stable	stable	Fatigue, weight loss, night sweats, palpable nodes and spleen

HGB, hemoglobin

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tired and less robust. His shotty cervical nodes were unchanged, but he had 2-3 cm palpable nodes in his axillae and his spleen tip was palpable approximately 3 cm below the costophrenic margin. CBC revealed a lymphocyte count of 160,000/ μL with stable hemoglobin and platelets. The disease had clearly advanced in several aspects. His lymphocyte count had increased, although the doubling time had slowed, with an increase of 40,000/ μL over a 2-year period. Often a patient complains of vague symptoms of fatigue that do not correlate with the amount of disease the patient exhibits. At this juncture, the patient's symptoms were undoubtedly attributable to his disease burden. His nodes and spleen had grown, and clear symptoms were now present affecting his quality of life.

Treatment

The patient began a regimen of fludarabine and rituximab (FR) for 4 cycles. This combination was chosen because it has been extremely effective in debulking and creating a meaningful remission.³ Two months after treatment, the patient was symptom free. His exam showed no evidence of disease. His CBC had normalized; he had a WBC of 4,000/ μL ; a lymphocyte count of 1,000/ μL ; ANC was normal; Hgb of 14 g/dL; and platelets of 250,000/ μL .

For the next 2 years, the patient felt well, though there was a small and gradual increase in the size of his nodes, spleen, and lymphocyte count. The rest of his CBC remained stable. He returned for a visit in 2007, 2 years since his treatment and 4 years since we first examined him for a second opinion (Table 1D). His systemic symptoms had returned, and he was experiencing severe night sweats and fatigue. He had lost 15 pounds. His exam showed 1-2 cm lymphadenopathy in his neck, axillae, and inguinal areas. His spleen was 6 cm below the costophrenic margin. CBC showed increased white cells of 180,000/ μL , predominantly lymphocytes. His Hgb level dropped to 8 g/dL and platelets to 130,000/ μL .

Table 1. Clinical features of an adult male with CLL (cont.)

D. At 2 years after initial treatment with 4 cycles of fludarabine and rituximab

Age (years)	WBC (μL)	Lymphocyte count (μL)	HGB (g/dL)	Platelets (μL)	Systemic Symptoms	Cytogenetic testing
56	180,000	160,000	8	130,000	Fatigue, weight loss, night sweats, palpable nodes and spleen	17p deletion

HGB, hemoglobin; mg, milligram; WBC, white blood count

We conducted a bone marrow biopsy because the patient was anemic out of proportion to the other counts, and we wanted to

understand the process causing the anemia. We also checked lactic dehydrogenase (LDH), Coombs, haptoglobin, and bilirubin levels. These tests confirmed that there was no hemolysis and his marrow was packed with CLL cells. The presence of hemolysis would have crucially affected the treatment prescribed.

The patient's disease had changed its behavior; he had developed severe symptoms. There was no dramatic change in his exam or CBC, yet the disease was affecting him in a dramatic fashion. He had significant adenopathy, but was not yet bulky. He also had moderate splenomegaly. Repeat cytogenetic testing revealed a new 17p deletion, which illustrates the changing biology of CLL, with newly acquired mutations developing during the disease course.

We recommended alemtuzumab 30mg 3 times a week. This treatment was chosen because it is particularly useful in this scenario: packed bone marrow, splenomegaly, nonbulky adenopathy, and the presence of 17p deletion, which indicates a greater likelihood of fludarabine resistance.⁴⁻⁶

Two months after completing week 12 of alemtuzumab, he had no symptoms; his adenopathy had gone down to less than 1 cm; his spleen shrunk to 2 cm below the costophrenic margin; and his CBC was almost normal.

Discussion

When we determined that it was time to treat the patient, we chose a front-line regimen of FR. Many physicians use fludarabine, cyclophosphamide, and rituximab (FCR) in the upfront setting based on MD Anderson data.⁷ MD Anderson published data using FCR in 224 chemotherapy-naïve patients. There was a 70% complete response (CR) rate and a 95% overall response (OR) rate. Although FCR has had impressive results in terms of relative response (RR) and CRs, it has never been shown to be superior to FR in a head-to-head trial. There is convincing evidence that combination therapy is superior to single-agent therapy. CALGB 9712 demonstrated benefit of concurrent FR vs sequential in terms of CR. Moreover, when compared to a historical group of patients treated with single-agent fludarabine in CALGB 9011 trial, the combination FR showed benefit in terms of CR, OR, 2 year over-all survival, and progression-free survival.⁸ It did not match FCR in terms of CR and RR, but patients were also spared FCR-associated myelotoxicity. Our philosophy is to use ammunition sparingly and save patients from additional toxicity when possible. Cyclophosphamide can be added in a later course of therapy when other combinations have lost efficacy.

The prognostic factors posed another confusing point. We checked mutations; CD38; ZAP-70; and FISH. Data from our patients over

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the past several years reveal an enormous discordance in these indicators. Therefore, it is important to view the available data in the context of each individual patient. If a patient is clinically ill, treatment should be given regardless of the prognostic markers. The reverse is true in a clinically healthy patient. The data for early treatment based on prognostic markers alone do not yet exist.

Several studies have demonstrated efficacy of alemtuzumab in the fludarabine-refractory patients. A pivotal multicenter trial demonstrated overall objective response to be 33% (CR 2%, PR 31%) with median time to progression of 4.7 months overall, 9.5 months for responders. Rai and colleagues published another multicenter study of alemtuzumab in 24 relapsed CLL patients.⁹ Eight (33%) achieved a partial remission with a median duration of response of 15.4 months. Median survival time was 35.8 months. An additional study found that patients with 17p deletion or mutation, a marker of fludarabine resistance, and aggressive disease had a 40% response rate with alemtuzumab.⁶

Summary

Chronic lymphocytic leukemia is a heterogeneous disease with a multitude of factors and scenarios that determine management. Treatment should be dictated foremost by the manifestation of symptoms and evidence of disease burden on the body. Conversely, treatment should not be started as a reflex to a certain number of lymphocytes. Treatment options include various chemoimmunotherapy combinations that typically include rituximab and fludarabine. Although impressive data exist on the efficacy of rituximab-cyclophosphamide and fludarabine, no head-to-head trial exists proving it superior to FR. FR is still an appropriate first-line combination. Alemtuzumab is also effective for nonbulky, fludarabine-refractory disease, even in the setting of 17p deletion. Table 2 explains the treatment options and reasoning for the recommendations used in this case.

Table 2. Rationale behind treatment decisions for a patient with CLL

Recommendation	Continued Observation	Fludarabine rituximab	Bone marrow biopsy	Alemtuzumab
Reasons for medication choice	Treatment should not be dictated by lymphocyte count or prognostic factors alone, but by quality of life	Treatment dictated by combination of large tumor burden and symptoms; FR combination effective in debulking	Useful to answer specific questions; Why is anemia proportionately more severe? Why was there a change in disease behavior?	Particularly useful in presence of packed bone marrow, splenomegaly, nonbulky adenopathy, 17p deletion
Things to consider before recommendation	Symptoms; lymphocyte doubling time; prognostic marker results	Lymphocyte count; presence of symptoms; quality of life	Change in disease behavior; severe symptoms; adenopathy; splenomegaly	Biology of the disease can change with the acquisition of new mutations (17p deletion)

FR, Fludarabine and rituximab

CASE 2. ACUTE LYMPHOBLASTIC LEUKEMIA

Cara Rosenbaum, MD; Richard Larson, MD

Background

Acute lymphoblastic leukemia (ALL) is the most common malignancy of childhood and adolescence, with approximately two-thirds of the 4,000 cases diagnosed annually in the United States seen in these age groups.¹⁰ Precursor B-cell ALL occurs both in children and in adults. Prospective studies have reported 5-year event-free survival (EFS) rates of approximately 80% in childhood and 40% in adult precursor B-cell ALL. Allogeneic stem cell transplantation (SCT) is rarely recommended for children with ALL in first complete remission (CR1). The optimal treatment strategy for adolescents and young adults has not been as clearly defined, given that historically this subgroup has represented a minority of the study participants enrolled onto either pediatric or adult protocols.¹¹ Another major subset of ALL patients in need of further prospective study includes adults with standard-risk features in whom the benefit of allogeneic SCT in CR1 remains unclear given conflicting data in the literature. Allogeneic SCT has been proven to benefit high-risk patients, yet its role remains less clearly defined in the standard-risk subset.

Case history

The patient is a 27-year-old Caucasian intensive care unit nurse who presented with increasing back pain, nausea, and generalized headaches. She had a past history of chronic neck and back pain and mitral valve prolapse. The patient's family history was noncontributory, and she had no full siblings. The patient's physical exam was unremarkable at presentation. The initial blood count showed a WBC count of 17,000/ μ L, hemoglobin of 12 g/dL, and platelets of 50,000/ μ L, with a lactic dehydrogenase level (LDH) of 7600 U/L.

The peripheral blood smear showed 35% circulating lymphoblasts. By flow cytometry, the circulating blasts were positive for TdT (terminal deoxynucleotidyl transferase), CD10, and CD19, and negative for CD20, surface immunoglobulin (sIg), and myeloid markers. Bone marrow aspiration showed hypercellularity with greater than 90% lymphoblasts. Bone marrow cytogenetics

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revealed only a deletion 6q abnormality in 2 metaphase cells. FISH showed no evidence of a *BCR-ABL* or *C-MYC* translocation. There was no central nervous system (CNS) involvement at diagnosis. A final diagnosis of common precursor B-cell ALL was made. Table 3 includes information on the clinical features of precursor B-cell acute lymphoblastic leukemia in this young adult.

Table 3. Clinical features of precursor B-cell ALL in a young adult

Age (years)	WBC (μ L)	PB blasts (%)	BM blasts (%)	CNS involvement	WHO	CD10	CD19	Tdt	No. of induction cycles	Clinical outcome	Current therapy
27	17,000	35	>90	No	Precursor B-cell	Pos	Pos	Pos	1	CR	Maintenance

BM, bone marrow; CNS, central nervous system; CR, complete remission; PB, peripheral blood; Tdt, terminal deoxynucleotidyl transferase; WBC, white blood count; WHO, World Health Organization classification

Treatment

The patient began therapy with the hyper-CVAD regimen and completed 1 course through day 14 without complications. On day 17, she relocated to Chicago to be closer to her family. Day 24 laboratory tests showed a WBC count of 3,100/ μ L with improvement in hemoglobin and platelet counts and no evidence of peripheral lymphoblasts. Day 28 bone marrow exam revealed the patient to be in morphologic remission with normal cytogenetics. A CR was thus achieved within 4 weeks after a single induction course. Discussion regarding further chemotherapy options ensued, specifically the use of a pediatric vs an adult regimen. A decision was made to follow a regimen being evaluated in the Children's Oncology Group (COG) AALL0232 phase 3 protocol for high-risk precursor B-ALL that includes patients aged 1 through 30 years. High risk in this protocol was defined as having a WBC count greater than 50,000/ μ L or age greater than 10 years.

The standard arm in this COG regimen features additional vincristine with PEG-asparaginase during consolidation, Capizzi-style escalating methotrexate during interim maintenance, and intrathecal methotrexate administered during each course. The patient began consolidation on day 36 and proceeded with interim maintenance. Periodic bone marrow examinations continued to show morphologic remission. Delayed intensification was then given with PEG-asparaginase and intrathecal methotrexate, followed by maintenance therapy given for 2 years from the start of interim maintenance. Presently, the patient continues on maintenance therapy and remains in CR1.

Discussion

This clinical case highlights 2 important evolving topics in the management of ALL: that of age and risk-adapted therapies. First, this case depicts a young adult treated successfully with an

intensive pediatric regimen by an adult oncologist, and second, shows that intensive multiagent therapy was completed without dose delays, reductions, or omissions.

Retrospective studies show that adolescents and young adults, specifically ages 15–20 years, have had better outcomes when

treated on intensive pediatric cooperative group protocols compared to adult ALL protocols, with 5-year EFS rates of approximately 60% vs 40%, respectively.¹¹ Specifically, 4 comparative studies have now been completed.^{12–15} These have

not been prospective randomized trials but retrospective studies from 4 different national groups comparing newly diagnosed ALL patients ages 15 to 20 years who were treated during contemporary periods of time on either pediatric or adult protocols. A variety of reasons may account for the differences seen in 5-year EFS rates, such as the specific chemotherapy agents used by pediatric versus adult groups, the management pattern of the physicians and nurses who administer the therapy, the adherence of patients to the treatment schedule, or the biological characteristics of the patients who go to pediatricians versus those who go to adult hematologist/oncologists.

There is reason to believe that a major difference may lie with the type of doctor chosen and not with the prescribed medication regimen. Adult oncologists have a different skill set compared to pediatric oncologists with regard to treating adolescents with ALL, and a large educational component exists in managing adolescents and young adults on strict pediatric regimens. The common goal for pediatric oncologists treating ALL is cure, whereas most adult oncologists commonly treat patients with metastatic solid tumors, for whom the goal is palliation. For instance, relatively little variance occurs in the scheduling of doses in pediatric protocols, while in the adult setting, protocol deviations are not an infrequent occurrence.

To test this hypothesis, a large phase 2 study (CALGB study 10403) has been designed as an intergroup study by the North American adult cooperative groups to utilize the COG pediatric front-line ALL regimen in newly diagnosed patients ages 16 to 30 years. In addition to toxicity and outcomes, demographic and socioeconomic data will be compared between patients treated in pediatric clinics and patients in the same age group treated in adult clinics. The objective will be to determine if adult oncologists following the same regimen

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as pediatric oncologists can achieve the same favorable outcomes in this group of patients.

The second major topic of discussion regarding the present case concerned the use of allogeneic SCT in CR1 in standard-risk ALL. This therapeutic option was discussed with the patient, who was HLA typed but had no siblings. Based on her favorable prognostic features of age less than 30 years, WBC count less than 30,000/ μ L for B-lineage ALL, and lack of the *BCR-ABL* transcript, she was deemed to be standard risk.¹⁶ Previous published studies have not suggested a survival benefit from allogeneic SCT in CR1 for adults with standard-risk ALL.^{17,18}

More recently, however, an abstract detailing outcomes from the MRC/ECOG E2993 trial reported that standard-risk adults who were recommended to receive a matched-sibling donor transplant in CR1 had improved 5-year OS rates of 63% vs 51%, respectively, in a donor versus no donor comparison.¹⁹ The strategy used in this trial was to transplant, if possible, all patients with an HLA-matched sibling in CR1. The control arm consisted of those without a donor who were then randomized either to additional chemotherapy alone or to an autologous transplant. The autologous transplant group did no better than the chemotherapy group, allowing a statistically significant difference in outcome to emerge between the donor and no donor groups. In contrast to earlier studies, a statistical advantage was observed in standard-risk patients receiving an allogeneic SCT, but not in high-risk patients or those older than 35 years.

The data presented in this trial conflict with data from large retrospective series and from prospective randomized trials that followed a similar design. They did not show an advantage to allogeneic SCT in standard-risk patients and did show an advantage in high-risk patients who were over the age of 35 or *BCR-ABL* positive.^{18,20,21} In the MRC/ECOG E2993 trial, a hypothesis for the better outcomes observed for patients with donors is that the no-donor control arm did unexpectedly worse compared to the donor arm. The 5-year OS of 51% in the no-donor control arm is inferior to the 3-year OS of 57% observed in a group of young adults 16-30 years old, including those with high-risk features who were treated with chemotherapy alone in sequential CALGB trials.²² Therefore, the optimal postremission strategy for standard-risk patients is not clear, and additional data from

prospective studies will be needed before one can decide if standard-risk ALL patients benefit from allogeneic SCT in CR1. Furthermore, if outcomes for standard-risk young adults are shown to improve markedly when treated with pediatric chemotherapy regimens, even more evidence may accumulate against using allogeneic SCT in CR1 for standard-risk patients compared to treatment with chemotherapy alone.

Summary

Through further prospective study of the adolescent and young adult population, we expect to gain more insight into optimal chemotherapy intensification and dose scheduling in the management of ALL in this subgroup and determine whether standard-risk patients are likely to benefit from allogeneic SCT in CR1.

CASE 3. MULTIPLE MYELOMA

Varant Arzoumanian, MD; Guido Tricot, MD

Background

Multiple myeloma is a cancer of the plasma cells. It is the second most prevalent blood cancer after non-Hodgkin's lymphoma. It tends to affect slightly more men than women. It generally has a poor prognosis. A skeletal survey is normally done to help in diagnosis of multiple myeloma. Bone marrow biopsies and cytogenetics may also be performed for prognostic purposes. Multiple myeloma treatment is generally aimed at containment and suppression.

Case history

The patient is a 62-year-old man diagnosed in May 2000 at the age of 55 years with IgA kappa multiple myeloma Durie Salmon stage IIA and ISS 1 (Table 4). At diagnosis he had a serum M of 2 g/dL, IgA of 3194 mg/dL, and no monoclonal proteins in urine by

Table 4. Clinical features of an adult male diagnosed with multiple myeloma

Age (yrs)	Serum M (g/dL)	IgA (mg/dL)	GEP	Monoclonal proteins	Plasma cell (%)	BM Biopsy			Durie Salmon stage	Bone densitometry	Skeletal Survey Fractures	MRI
						Plasma cell (%)	Cells in S phase (%)	Plasma cell labeling index (%)				
55	2	3194	High expression in quartile 4 of FGFR3	none	33	33	2.8	0.8	IIA ISS 1	Severe osteoporosis	T6, T8 No lytic lesions	No spine myeloma lesions in posterior iliac bones bilaterally

BM, bone marrow; GEP, gene expression profile; MRI, magnetic resonance imaging

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electrophoresis and immunofixation. He had normal albumin and LDH. Bone marrow biopsy showed 33% plasma cells, 2.8 % cells in S phase, and 0.8% plasma cell labeling index. Metaphase cytogenetics were normal. Gene expression profiling (GEP) showed high expression in quartile 4 of FGFR3, indicating the presence of t(4;14). Based on bone densitometry, severe osteoporosis was diagnosed. Skeletal survey showed fractures involving T6 and T8, but no lytic lesions. Therefore, these fractures could have been secondary to osteoporosis. Magnetic resonance image (MRI) of the pelvis and the spine showed no myeloma lesions in the spine, but some focal lesions in the posterior iliac bones bilaterally.

If skeletal survey were the only modality to evaluate bone involvement, we would have missed symptomatic myeloma, and therefore myeloma requiring treatment. In the setting of normal hemoglobin, creatinine, and negative skeletal survey, the diagnosis would have been smoldering myeloma. The standard prognostic factors for risk stratification, which include B2-microglobulin and albumin, indicate that the patient falls in the low-risk group ISS 1.²³ However, based on GEP, the patient had features of high-risk disease, as evidenced by high expression of FGFR3.²⁴

Treatment

The patient was enrolled in the Total Therapy II protocol at the University of Arkansas and randomized to the no thalidomide arm.²⁵ He received a tandem transplant with melphalan 200 mg/m² as a preparative regimen in October 2000. In February 2001, he achieved CR. The patient received maintenance with dexamethasone for a year. He initially received standard pulsing every month, and after the second year, he received standard pulsing every 3 months. He remained in CR for almost 6 years after his first transplant.

In August 2006, he showed slowly progressive disease as evidenced by a monoclonal spike on serum electrophoresis, increasing IgA levels, and an increase in bone marrow plasmacytosis. His GEP again showed high expression in quartile 4 of FGFR3. He received bortezomib, thalidomide, dexamethasone (VTD) as salvage therapy. After 3 cycles, he again achieved CR, and as of May 2007, he continued to be in CR, with negative immunofixations, normal bone marrow, and negative PET scans.

Discussion

There are 4 treatment options in cases like this: thalidomide and dexamethasone; melphalan, prednisone, thalidomide (MPT); VTD;

and intensive induction treatment with stem cell support. Thalidomide and dexamethasone is an effective regimen in newly diagnosed myeloma patients with response rates around 60%.²⁶

Two studies have shown the efficacy of MPT in newly diagnosed patients. Palumbo and colleagues in the Italian Myeloma Group showed a response rate reaching 78%.²⁷ In a 3-arm randomized study, the French group showed the superiority of MPT compared to melphalan and prednisone (MP) and to low-dose melphalan 100 mg tandem transplant in elderly patients.²⁸

VTD has shown efficacy in phase 2 trials.²⁹ Wang and colleagues at MD Anderson have shown response rates in excess of 85% with CR approaching 20% in newly diagnosed patients. Barlogie and colleagues have used this combination in newly diagnosed patients and as maintenance with minimal toxicity and impressive results.³⁰ High-dose therapy with tandem stem cell transplant support is still considered the standard of care in patients less than 60 years old, especially those not achieving a very good partial response.^{31,32}

In multiple myeloma, any kind of cytogenetic abnormality detected by metaphase analysis indicates a poor prognosis. GEP based on biologic features classifies myeloma patients into 7 subgroups. Those with a proliferation profile or overexpression of MMSET (the FGFR3 group) or MAF translocations (14;16) and (14;20) have an inferior outcome.^{33,34} Patients with cyclin D1 oncogene or with hyperdiploid features without a proliferation pattern have a good outcome. In the Total Therapy I study, about 20% of the patients are still in complete remission more than 10 years after their first transplant. GEP can show that although these patients are in long-term complete remission, 14 of the 18 long-term survivors of more than 10 years still had monoclonal gammopathy of undetermined significance (MGUS)-like features. Evidence of disease remained in most patients in spite of their long-term remissions. Only 4 of those patients had completely normal gene arrays.

To simplify the analysis, investigators analyzed a much smaller 70-gene model, which allowed the stratification of patients into low-risk (87%) and high-risk disease (13%).³⁴ Half of the patients transplanted were alive at 5 years. Patients with the 70-gene low-risk profile fared much better than those with the high-risk profile.

Translocations involving the immunoglobulin heavy chain locus on 14q32: t(4;14) (14;16) and (14;20) also confer a poor prognosis.³⁵ Such translocations, involving the terminal fragments of chromosomes, can only be detected by fluorescence in situ hybridization

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(FISH). These translocations are highly represented in cases with hypodiploidy and deletion of chromosome 13.³⁶ The t(4; 14) is usually a translocation of the receptor of tyrosine kinase FGFR3 to the immunoglobulin heavy chain switch region locus. This is found in almost 15% of patients with multiple myeloma.³⁷ It identifies a subset of patients with significantly shorter time to progression and also shorter overall survival. In the Total Therapy I study by Barlogie and colleagues, patients without cytogenetic abnormalities had a 10-year survival of about 40%. Survival was clearly inferior in patients who had cytogenetic abnormalities.³⁸ Those with deletion of chromosome 13 or hypodiploidy fared much worse than patients with other cytogenetic abnormalities, mainly hyperdiploid abnormalities.

This has been shown to be a more powerful predictor of outcome than the deletion 13 as detected by FISH (50% of patients).³⁹ The FISH detection of the deletion of chromosome 13 is considered by many as either a weak predictor of outcome or as having no prognostic significance at all, but the deletion of chromosome 13 detected by metaphase analysis (17% of patients) still retains its negative prognostic value.

Based on more than 1500 patients enrolled in several trials, some authors have concluded that those who carry t(4;14) may have minimal or no benefit from autologous stem cell transplant and need novel therapeutic approaches.⁴⁰ The data on allotransplantation in multiple myeloma has not been very good in high-risk patients. High-risk patients with multiple myeloma who receive an allotransplant either develop graft-versus-host disease with all its associated problems, or if they do not, they have no benefit of an allogeneic over autologous transplant.⁴¹

An Italian study by Bruno and colleagues was randomized according to whether patients had matching donors. Patients with a matching donor received allotransplants, while those without matches received tandem autologous transplants.⁴² The survival rate of the patients who received allotransplantation from an HLA-identical sibling was superior to that of the recipients of autologous transplants. However, t(4;14) need not necessarily be disastrous. Half of the patients exhibiting t(4;14) lived 5 years or longer with a tandem transplant approach, which is much better than with any other therapy at this point in time.

Summary

This case presents the importance of skeletal survey and gene profiling. A skeletal survey, which is still considered the standard

imaging procedure, can miss bone disease in multiple myeloma. It is an outdated technique, and bone involvement in myeloma should be assessed by either MRI or PET/CT scan. This patient would not have been treated and consequently would not have reached long-term disease-free survival if therapy were delayed. It is our experience that as many as 100 or more lesions can be found on PET scans even when the skeletal survey is negative.

The second important message is related to gene profiling. Patients with good prognosis based on standard prognostic markers may be found to have aggressive disease based on GEP. Alternatively, a subgroup of patients considered to have poor prognosis by FISH may do much better after taking into consideration the GEP data. The outcome of high-risk patients can be further improved with the use of new agents such as bortezomib and lenalidomide, either at the time of relapse or as maintenance therapy after transplantation.

CASE 4. NON-HODGKIN'S LYMPHOMA

Erick Lansigan, MD; Francine Foss, MD

Background

Follicular lymphoma (FL) is the second most common non-Hodgkin's lymphoma (NHL) and comprises ~25% of NHL according to the World Health Organization classification.⁴³ Based on data from the last 30 years, FL is an indolent disease with a median survival of 10 years. More recent data suggest that with improvements in treatment, the median survival is 12-14 years.⁴⁴

The Follicular Lymphoma International Prognostic Index (FLIPI) is a useful prognostic tool.⁴⁵ It classifies patients into low-, intermediate- and high-risk groups based on the presence of 5 risk factors: age > 60 years, Ann Arbor stage III-IV, hemoglobin <12g/dL, number of nodal areas >4, and serum LDH above normal. Patients in the low-risk group (0-1 adverse factors) have a 10-year overall survival (OS) of 71%; patients in the intermediate-risk group (2 adverse factors) have a 10-year OS of 51%; and patients in the high-risk group (>3 adverse factors) have a 10-year OS of 36%. A recent abstract from ASCO 2007⁴⁶ validated the FLIPI in a prospective fashion in the era of rituximab. The 3-year progression-free survival was 81%, 62%, and 50% for patients at low-risk, intermediate-risk, and high-risk, treated with rituximab plus chemotherapy, and 76%, 56%, and 43% in those treated with chemotherapy only ($P<0.001$).

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Table 5. Clinical features of an adult male diagnosed with non-Hodgkin's lymphoma

A. At time of diagnosis

Age (yrs)	WBC (μL)	HGB (g/dL)	Plts (μL)	LDH	Beta 2 micro-globulin	Flow cytometry					BM biopsy			Pet scan
						CD 19	CD 20	CD 23	CD 10	CD 5	BCL2	BCL6	% marrow involvement with Lymphoma	
37	6000	15.6	279,000	norm	2.41	+	+	+	+	-	+	+	10	Increased activity in most major nodal groups

BM, bone marrow; HGB, hemoglobin; LDH, lactate dehydrogenase; norm, normal; WBC, white blood count

Case history

A 38-year-old man presented 14 months ago to his primary doctor with cough and wheezing for several weeks (Table 5A). He was given a course of antibiotics. However, he was noted to have persistent left neck adenopathy. A CT scan showed multiple areas of lymphadenopathy in cervical, supraclavicular, axillary, mediastinal, retroperitoneal, mesenteric, inguinal, and subcarinal lymph nodes. He underwent a left neck excisional lymph node biopsy that revealed nodular proliferation of small lymphocytes with irregular cleaved nuclei and irregular nuclear membranes. Immunostains and flow cytometry were positive for CD10, CD19, CD20, and CD23, and negative for CD5, and were felt to be consistent with a low-grade follicular center lymphoma.

His white count was 6,000/ μL with a normal differential, hemoglobin 15.6 g/dL, and platelets 279,000/ μL . LDH was normal. Beta 2

Figure 1. CT scan showing follicular lymphoma

This CT scan of a 37-year-old man with follicular lymphoma showed a large retroperitoneal mass that had increased in size compared to his prior scan with vascular encasement and left hydronephrosis.



microglobulin was 2.41 mg/L (slightly elevated), and he had no B symptoms. A bone marrow biopsy showed a normocellular marrow with atypical lymphoid aggregates that was again CD20 positive and CD10 positive, consistent with follicular lymphoma. BCL2 and BCL6 were positive, and 10% of the marrow was involved with lymphoma. He had a PET scan

that showed markedly increased activity in most major nodal groups as well as dramatic uptake in the para-aortic and caval retroperitoneal nodes with SUV of 15.

His local oncologist and the patient decided to take a watch-and-wait approach. However, 2 months later, he developed symptoms of chest pressure and discomfort in the groin, and a CT scan showed worsening lymphadenopathy. A decision was made to give the patient 4 weekly treatments of rituximab therapy, and he had symptomatic improvement and regression of his adenopathy. He was then closely observed.

Six months later, the patient noted increase in size of his left neck and right groin adenopathy and came for a second opinion at Yale University Comprehensive Cancer Center. At that point, rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) was recommended. After 5 cycles of R-CHOP, he complained of fevers and night sweats, and a CT scan showed a large retroperitoneal mass that had increased in size compared to his prior scan with vascular encasement and left hydronephrosis (Figure 1).

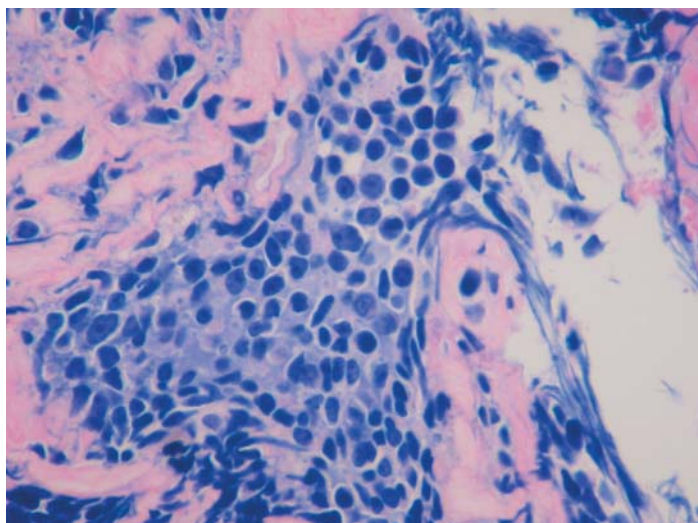
He had a nephrostomy tube placed, and his retroperitoneal mass was biopsied (Figure 2, page 11) and showed lymphoid elements with relatively abundant cytoplasm, hyperchromatic nuclei, and focally prominent nucleoli (Figure 2, page 11). The immunohistochemical stains were positive for CD10, BCL2, and CD43, and were negative for BCL6 and CD3. The proliferative index, estimated by stain for KI-67, was approximately 70%. In summary, given these morphological and immunohistochemical findings, his clinical picture was consistent with transformation to a diffuse large B-cell lymphoma (DLBCL) (Table 5B, page 11).

Treatment

This patient, with an intermediate-risk FLIPI of 2, was initially treated with 4 weekly infusions of single-agent rituximab

Figure 2. Morphology and immunohistochemistry of diffuse large B-cell lymphoma

Abundant cytoplasm, hyperchromatic nuclei, and focally prominent nucleoli are seen here in this biopsy of a retroperitoneal mass in a man with diffuse large B-cell lymphoma. The immunohistochemical stains were positive for CD10, BCL2, and CD43, and were negative for BCL6 and CD3. The proliferative index, estimated by stain for Ki-67, was approximately 70%.



375mg/m² (Table 6, page 12), although there were concerning findings on PET scan that will be discussed later. This approach was prospectively studied by Colombat et al who reported that 50 patients with low tumor burden, no nodal or extranodal involvement of more than 7cm, showed a response rate (RR) of 73% after 1 month of treatment, and a durable molecular response at one year of 62%.⁴⁷ Rituximab as a single-agent was also studied by Hainsworth et al⁴⁸ in patients with bulky disease who required therapy. The RR after 4 infusions of rituximab was 37%. However,

Table 5. Clinical features of an adult male diagnosed with non-Hodgkin's lymphoma

B. At time of diagnosis with diffuse large B-cell lymphoma

Age (yrs)	Biopsy of retroperitoneal mass	Proliferative index percentage	Immunohistochemical stains				
			CD3	CD10	CD43	BCL2	BCL6
38	Lymphoid elements with relatively abundant cytoplasm, hyperchromatic nuclei, focally prominent nucleoli	70	-	+	+	+	-

this increased to 73% after subsequent cycles of rituximab. Nevertheless, rituximab, although active as a single-agent, is of limited use, especially in patients with bulky lymphadenopathy.

For patients with a high FLIPI score, symptomatic disease, bulky lymph nodes, and/or splenomegaly, or rapid disease progression, rituximab with cytotoxic chemotherapy is favored. Several randomized trials have shown that the addition of rituximab to chemotherapy results in higher RR and longer time to progression and event-free survival in first-line FL or first relapse (Table 6, page 12). For example, a randomized study of 8 cycles of cyclophosphamide, vincristine, and prednisone (CVP) vs R-CVP⁴⁹ showed that the OR and CR were 81% and 41% in the R-CVP arm compared to 57% and 10% in the CVP only arm, respectively. Median time to treatment failure was 27 months in patients receiving R-CVP and 7 months in the CVP arm. This trial also showed a trend toward improvement in OS in the R-CVP arm. Similarly, the German Low-Grade Lymphoma Study Group (GLGLSG) showed in a randomized trial that R-CHOP was superior to CHOP with improved response rates (96% vs 90%), and longer time to treatment failure (not reached vs 31 months).⁵⁰ Thus, it is widely accepted that rituximab added to chemotherapy is better than chemotherapy alone.

The choice of front-line regimen is highly variable, however. While fludarabine based-regimens are also highly effective in the first-line setting as well as in relapsing patients (Table 6, page 12),⁵¹⁻⁵⁴ stem cell mobilization may be impaired for future autologous stem cell transplants.

Discussion

A few features make this case atypical and are worth mentioning. This patient presented at a young age; the median age at presentation of FL is age 65.⁴³ This patient's symptoms progressed after only 2 months of observation; FL usually follows an indolent course. The initial bone marrow biopsy showed BCL2+, consistent with FL; however, BCL6 was also positive, a less common feature of FL, and considering a broader differential diagnosis, could indicate germinal center DLBCL. The high FDG uptake in the retroperitoneum

probably should have prompted a biopsy earlier in his course to determine if another process, such as transformation, was occurring. Given these features, chemotherapy with CVP and rituximab would have been a reasonable initial therapy in this

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Table 6. Selected studies with rituximab

Reference, number of patients	Regimen		p-value
First-line patients			
Colombat et al. (2001), n=49 Response rate Time to progression	Rituximab in low-burden FL 73% 13 months		N/A
Hainsworth et al. (2002), n=62 Response rate Progression-free survival	Rituximab in indolent lymphoma 43%§ / 73%* 34 months		N/A
Marcus et al. (2005), n=321 Response rate Median time to treatment failure	CVP 57% 7 months	R-CVP 81% 27 months	p<0.0001 p<0.0001
Hiddemann et al. (2005a), n=428 Response rate Median time to treatment failure	CHOP 90% 31 months	R-CHOP 96% Not reached	p=0.011 p<0.0001
McLaughlin et al. (2003), n=149 Response rate 3-year progression-free survival	Sequential FND+R for indolent Lymphomas 95% 64% / 59% ψ	Concurrent R+FND for indolent Lymphomas 100% 77% / 84% ψ	p=0.17 p=0.11 / p=0.01 ψ
Czuczman et al. (2005), n=40 Response rate Progression-free survival	Fludarabine + R 90% 40+ months		N/A
Relapsing patients			
Wierda et al. (2005), n=177 Response rate Time to progression	FC-R† 73% 28 months		N/A
Forstpointner et al. (2004, 2006), n=147 Response rate Time to progression	FCM 58% 10 months	R-FCM 79% 16 months	p<0.01 p<0.01

§ at 6 weeks, after 4 weekly doses of rituximab; * after maintenance rituximab; ψ follicular lymphoma subset; † reported for CLL/SLL patients; Abbreviations: R, rituximab; CVP, cyclophosphamide, vincristine, prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; FND, fludarabine, mitoxantrone, dexamethasone; FC, fludarabine, cyclophosphamide; FCM, fludarabine, cyclophosphamide, mitoxantrone

patient, though R-CHOP also could have been considered if an initial biopsy showed more aggressive disease. Anthracyclines are indicated for grade 3 FL, DLBCL, or transformed FL. Other features to be aware of that may indicate transformation are the presence of B symptoms, rapidly growing lymph nodes, rising LDH, cytopenias, and recurrent or serious infections.

Transformation of FL to a high-grade lymphoma

The reported incidence of histologic transformation (HT) ranges from 16% to 60% depending on length of follow-up and whether rebiopsy or autopsy was performed. A recent study shows the HT rate to be 28% at 10 years.⁵⁵ Factors that seem to predict transformation are advanced stage and high-risk FLIPI or IPI scores at diagnosis. Expectant management, older age, low hemoglobin level, and high LDH also are associated with a higher risk of HT. The median survival from the time of transformation is 11 months. When an indolent lymphoma transforms, aggressive treatment is

warranted. Upon review of physician practices, many oncologists treat with an anthracycline-based regimen in anthracycline naïve patients.⁵⁵ If R-CHOP has been exhausted, appropriate salvage treatment options are ifosfamide, carboplatin, and etoposide (ICE); infusional etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin (EPOCH); dexamethasone, high-dose ara-C, and cisplatin (DHAP); or etoposide, methylprednisolone, high dose ara-C, and cisplatin (ESHAP).

Recently, radioactive immunotherapy (RIT) has been approved for use in transformed B-cell lymphoma, but has been underutilized. Tositumomab iodine-131 (Bexxar) and ibritumomab tiuxetan Y-90 (Zevalin) are radioimmunoconjugates targeting the CD20 antigen. In a pivotal multicenter phase 3 study, 60 patients with extensively

pretreated refractory indolent NHL and transformed NHL were treated with I-131 tositumomab, achieving an overall response rate of 65% and CR rate of 20%.⁵⁶ The median duration of response for complete responders was not reached at 47 months of follow-up. A randomized controlled clinical trial compared Y-90 ibritumomab vs rituximab (375 mg/m² weekly for 4 doses) in 143 patients with relapsed or refractory low-grade follicular lymphoma/transformed NHL.⁵⁷ Y-90 ibritumomab proved statistically superior, with an overall response rate of 80% compared to 56% in the rituximab arm. Similarly, CR was 30% in the RIT group vs 16% in the rituximab group. These 2 studies showed that single-agent RIT has clinical efficacy even when rituximab has failed. Since this therapy requires the administration of radioisotopes, a nuclear medicine or radiation oncologist specialist is required. Lastly, the use of RIT to consolidate response and as an in vivo purge prior to ASCT has been shown to be safe and effective.^{58,59} A phase 3 trial of tositumomab + high-dose carmustine, etoposide, cytarabine, and melphalan (BEAM) vs rituximab + BEAM is underway.⁶⁰

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Summary

To date this patient has received salvage therapy with R-ICE and R-DHAP, and still has some residual disease in the retroperitoneum. He is being considered for RIT in combination with high-dose chemotherapy and autologous stem cell rescue. Given his young age and the overall poor prognosis of HT, consolidation with an allogeneic transplant could be considered.

CASE 5. HODGKIN'S LYMPHOMA

Wei Lin, MD; Anas Younes, MD

Background

In 1832, Thomas Hodgkin first described Hodgkin's lymphoma, or Hodgkin's disease. Hodgkin's lymphoma is clinically characterized by the orderly spread of the disease from one lymph node group to another and the development of systemic systems with advanced disease. It is one of the most curable forms of cancer, with a cure rate of about 93%. Hodgkin's lymphoma was one of the first cancers to be cured by radiation, and also one of the first to be cured by combination chemotherapy. Hodgkin's lymphoma usually occurs in either young adulthood (15–35 years) or people over age 55 years. Approximately 1 in every 25,000 people is diagnosed with Hodgkin's lymphoma annually. More men than women have Hodgkin's lymphoma, but the nodular sclerosis variant is more common in women.

Case History

A 47-year-old woman presented to MD Anderson Cancer Center in relapse from Hodgkin's lymphoma. In 2002 she was diagnosed with stage IVB classical Hodgkin's lymphoma, nodular sclerosis type with an International Prognostic Score (IPS) of 4, (age over 45 years, stage IV disease, white blood cell count over 20,000/mm³, and

lymphocyte count under 600/mm³) (Table 7). She was treated at an outside hospital with adriamycin, bleomycin, vinblastine, dacarbazine (ABVD) for 6 cycles, and achieved a complete remission (CR) that lasted for only 3 months. Subsequently, she received dexamethasone, high-dose cytarabine, and cisplatin (DHAP) with no response. Her therapy was then changed to ifosfamide, carboplatin, etoposide (ICE), which was followed by high-dose chemotherapy and autologous stem cell rescue. Unfortunately, she relapsed again 7 months later. She was re-treated with ICE followed by an allogeneic stem cell transplant. Her brother was a fully matched donor. She remained in remission for the next 12 months, without significant graft-versus-host disease (GVHD).

Treatment

Upon her third relapse, she presented to MD Anderson for treatment options. She was asymptomatic upon presentation. Her physical examination was unremarkable, without palpable lymph nodes. Complete blood counts were within normal limits, as were renal function and liver function. Her positron emission tomography-computed tomography (PET-CT) scan revealed bilateral cervical lymph node involvement, a subpectoral nodule, a right hilar lymph node, a right pulmonary nodule, and a retroperitoneal lymph node. A biopsy of the pulmonary nodule demonstrated recurrent classical Hodgkin's lymphoma. Bilateral bone marrow biopsies with flow cytometry were negative for evidence of disease.

Discussion

This case highlights several important decision points in the management of Hodgkin's lymphoma. This discussion focuses on the use of prognostic factors, the initial therapy for advanced Hodgkin's lymphoma, the therapy for relapsed disease, and the emerging role of PET scans for staging and monitoring of therapy.

Prognostic factors

The international prognostic score (IPS) uses 7 factors to identify patients who are at high risk for poor outcome.⁶¹ These factors include serum albumin level under 4.0g/dL, hemoglobin under 10.5 g/dL, male gender, age over or equal to 45 years, stage IV disease,

Table 7. Clinical features at diagnosis of an adult female with Hodgkin's lymphoma

Age (yrs)	IPS	Ann Arbor Stage	WBC (/ μ L)	Lymphocyte count (mm ³)	1st Tx	Clinical outcome (duration)	2nd Tx	Clinical outcome (duration)	3rd Tx	Clinical outcome (duration)	4th Tx	Clinical outcome (duration)
42	4	IVB classical	>20,000	<600	6 cycles ABVD	CR (3 months)	DHAP	No response	ICE highdose chemotherapy autologous stem cell rescue	CR (7 months)	Allogeneic stem cell transplant	Remission (12 months)

ABVD, adriamycin, bleomycin, vinblastine, dacarbazine; CR, complete remission; DHAP, dexamethasone, high-dose cytarabine, and cisplatin; ICE, ifosfamide, carboplatin, etoposide; IPS, International Prognostic Score; tx, treatment

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white cell count over or equal to 15,000/ μ L, and lymphocyte count under 600/ μ L or under 8%. With an increasing number of

Table 8. Outcome at 5 years according to International Prognostic Score⁶⁰

Number of Factors	Progression Free Survival	Overall Survival
0	84%	89%
1	77%	90%
2	67%	81%
3	60%	78%
4	51%	61%
≤ 5	42%	56%

factors, the event-free survival at 5 years declines (Table 8). In clinical practice, IPS has been used only for prognosis and not for management. Specifically, at the present time there is no evidence to support the use of a more aggressive treatment regimen for high-risk patients based on the IPS score.

Initial Therapy

The standard first-line therapy for Hodgkin's lymphoma is a doxorubicin-containing regimen. In North America, ABVD is the most widely used first-line therapy for patients presenting with advanced (stage III-IV) Hodgkin's lymphoma. ABVD has been shown to be superior to mustargen, vincristine, procarbazine, and prednisone (MOPP), with 5-year overall survival of 82% and progression-free survival of 63%.⁶² The shortened, more dose-intensive regimen Stanford V (doxorubicin, vinblastine, mechlorethamine, vincristine, bleomycin, etoposide, and prednisone) with involved field radiation therapy has demonstrated a 5-year overall survival of 96% and a progression-free survival of 89%.⁶³ However, this regimen is not as widely used as ABVD, and definitive randomized clinical trials comparing the 2 regimens are still ongoing. Similarly, the BEACOPP regimen (bleomycin, etoposide, doxorubicin,

Table 9. Response rates of various chemotherapeutic regimens in advanced Hodgkin's lymphoma

Regimens	Complete Response
ABVD	80%
MOPP/ABV	76%
Stanford V	72%
COPP/ABVD	85%
BEACOPP	88%
High-dose BEACOPP	96%

ABV, adriamycin, bleomycin, vinblastine; ABVD, adriamycin, bleomycin, vinblastine, dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; COPP, cyclophosphamide, and prednisone; Stanford V, doxorubicin, vinblastine, mechlorethamine, vincristine, bleomycin, etoposide, and prednisone.

cyclophosphamide, vincristine, procarbazine, and prednisone) has been shown to have promising activity and is currently being prospectively compared to ABVD in a randomized study. However, it is also not as widely used as ABVD due to increased toxicity. The response rates for the various regimens are listed in Table 9.

Therapy for relapsed disease

Based on 2 randomized trials, salvage therapy followed by autologous stem cell transplant is considered the standard of care for patients with relapsed and refractory Hodgkin's lymphoma.^{64,65} The most widely used salvage regimens are platinum-based, such as ICE, DHAP, or ESHAP (etoposide, methylprednisolone, high-dose cytarabine and cisplatin).⁶⁶⁻⁶⁸ Gemcitabine-based regimens such as GND (gemcitabine, vinorelbine, and pegylated liposomal doxorubicin) and IGeV (ifosamide, gemcitabine, and vinorelbine) are also used with reported high remission rates.⁶⁹ Studies have identified systemic symptoms at relapse, extranodal disease, and short (under 1 year) remission as poor prognostic factors for transplant outcome.⁷⁰

The management of relapsed Hodgkin's lymphoma after autologous stem cell transplant remains challenging. In recent years, increasing numbers of patients are considered for allogeneic stem cell transplant, although this approach remains experimental. Other options include experimental therapy using novel small molecules and immunotherapy.

PET scan in monitoring response

Accumulating evidence suggests that a positive PET scan after 2 cycles of therapy is predictive of poor outcome after ABVD therapy.⁷¹ This observation raised the possibility of designing new treatment approaches based on early PET scan results. However, as of today, there is no evidence that changing chemotherapy regimen in the setting of a positive PET after 2 cycles will change the outcome, and this question should be addressed only in clinical trials.

Summary

In summary, this 47-year-old woman was treated with ABVD and achieved a CR for 3 months. Upon first relapse, she received salvage therapy with ICE and autologous stem cell transplant and achieved a CR for 7 months. Upon second relapse, she received salvage therapy again with ICE and then allogeneic stem cell transplant. She had a third relapse after 12 months. There are several different decision points in the management

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of Hodgkin's lymphoma that require further investigation. These different decision points include the use of prognostic factors, the initial therapy for advanced Hodgkin's lymphoma, the therapy for relapsed disease, and the emerging role of PET scans for staging and monitoring therapy.

Conclusion

As these various cases have shown, diagnostic issues and treatment choices are not at all clear-cut in the lymphoid malignancies, whether physicians have practiced for years or are relatively new to their specialties. They grapple with such questions as when to begin treatment, with what agents, and how much to depend on prognostic markers, as demonstrated in particular by the case study on CLL.

Interpreting the data from an ever-increasing body of evidence is difficult and often contradictory. In ALL, there is now evidence that treating young adults with a pediatric regimen is more effective; the issue then arises whether a pediatric or adult specialist should

be in charge of the treatment. On the other hand, it is still not clear whether stem cell transplant for standard-risk ALL patients in first remission is beneficial.

In multiple myeloma, the importance of gene profiling is demonstrated by the case presented, as well as the argument for determining bone involvement by MRI or PET/CT. The discussion of follicular lymphoma brings to light the particular complexities of treating the disease when its presentation is atypical, in this case aggressive disease occurring in a young person. And these issues surrounding prognostic factors, initial therapy, treatment for relapsed disease, and the emerging role of different technologies for staging and monitoring therapy are still important decision points in treating Hodgkin's lymphoma, one of the most curable forms of cancer. It is apparent from these case studies that while the diseases may be classified together as lymphoid 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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