Risk Analysis in the Treatment of Hematologic Malignancies in the Elderly

SANDRA KURTIN, RN, MS, AOCN®, ANP-C

From the University of Arizona and Arizona Cancer Center, Tucson, AZ.

The author has no conflicts of interest to disclose.

Correspondence to: Sandra Kurtin, RN, MS, AOCN, ANP-C, Arizona Cancer Center, 3838 N. Campbell Ave, Tucson, AZ 85719. E-mail: skurtin@umcaz.edu

Abstract

Chronic lymphocytic leukemia (CLL), non-Hodgkin's lymphoma (NHL), multiple myeloma (MM), acute myelogenous leukemia (AML), and myelodysplastic syndromes (MDS) represent the most common hematologic diseases in adults, with the majority of diagnoses in patients over the age of 65. Older adults (> 65 years) are expected to exceed 20% of the overall U.S. population by the year 2030. Given the predicted increase in the size of the older adult population along with the incidence of these cancers, health care providers must familiarize themselves with the needs of older adults with hematologic malignancies. Risk-adapted treatment approaches include primarily disease-specific prognostication. The effect of comorbidities and functional status on treatment outcomes has been evaluated in recent clinical trials. Functional decline is associated with loss of independence and decreased quality of life. Most of these hematologic diseases are not curable; therefore, the preservation of quality of life and independent function should remain a priority. Careful consideration of the patient and disease-related factors together with the expectations of the patient and the consistent availability of caregivers is necessary to provide the best outcome. Familiarity with recent clinical trials data, risk-adapted treatment guidelines, and the complex attributes of the older adult will provide the advanced practitioner sound clinical management strategies and effectively eliminate chronologic age alone as a barrier to treatment of common hematologic malignancies.

J Adv Pract Oncol 2010;1:19–29

Advanced age is a leading risk factor for developing cancer. Older adults (> 65 years) are expected to exceed 20% of the overall U.S. population by the year 2030 (Jemal et al., 2009). Approximately 60% of all new cancer diagnoses are attributed to older adults, with this number expected to reach 85% by 2030 (Lichtman, Balducci, & Aapro, 2007).

Chronic lymphocytic leukemia (CLL), non-Hodgkin's lymphoma (NHL), multiple myeloma (MM), acute myelogenous leukemia (AML), and myelodysplastic syndromes (MDS) represent the most common hematologic diseases in adults, with the majority of these diagnoses in patients over the age of 65 (Table 1). Most

Table 1. Epidemiology for common hematologic malignancies

Disease	New cases (U.S., 2009)	Deaths (U.S., 2009)	Median age at diagnosis (years)	5-Year relative survival rate, 1996–2004[a]
NHL	63,000	18,600	67	65%
MM	20,580	10,580	65	35%
CLL	15,490	4,390	72	76%
AML	12,810	9,000	67	22%
MDS	9,730	N/A	70	45%[b]
CML	5,050	470	66	50%

Note: NHL = Non-Hodgkin's lymphoma; MM = multiple myeloma; CLL = chronic lymphocytic leukemia; AML = acute myelogenous leukemia; MDS = myelodysplastic syndromes; N/A = not applicable; CML = chronic myelogenous leukemia. From Jemal et al., 2009, Kurtin, 2010. [a]Excludes myelodysplastic syndromes. [b]Represents a 3-year survival rate.

of these cancers are not curable but are highly treatable. Known risk factors for each disease vary; hematopoietic senescence, a normal part of aging, is thought to play a role. These diseases represent a group of heterogeneous myeloid or lymphoid clonal stem-cell disorders with variable clinical presentation, pathologic characteristics, prognosis, and recommended treatment (Kurtin, 2010). Researchers have developed and continue to refine prognostic tools based on the characteristics of these diseases (Table 2). Given the predicted increase in size of the older adult population along with the incidence of these cancers, health care providers must familiarize themselves with the needs of older adults with hematologic malignancies.

Cancer is the leading cause of death in both men and women aged 60–79 years, yet life expectancy with independent function is 15 years for a person 65 years of age, 10 years for persons age 75, and 6 years for persons 85 years of age (U.S. Social Security Administration, 2009). Death rates from lymphoma, the most common hematologic malignancy, have decreased by 19% for women and 12% for men between 1991 and 2005. Death rates for MM (11.3% for women, 7.3% for men) and leukemia (14.5% for women, 9.4% for men) have also declined (Jemal et al., 2009). These rates are reported as generalized numbers without consideration of the heterogeneity of each disease. Additionally, older adults represent a heterogeneous group with variability in physiologic function and cultural, sociologic, and economic factors, each of which may affect treatment decisions and tolerance (Given & Given, 2008).

Historically, older adults have been underrepresented in clinical trials, particularly registration trials for new drugs or new indications in cancer treatment (Talarico, Chen, & Pazdur, 2004). Therefore, it is difficult to generalize trial results to individual patients or age groups. Clinical trials conducted since 2005 have provided improved diagnostics, established risk-stratified treatment guidelines, introduced novel therapies, and refined supportive care strategies, resulting in improved overall response rates (ORR), overall survival (OS), disease control, and quality of life for patients with common hematologic malignancies.

More recent trials do not include advanced age in the exclusion criteria for participation. However, barriers to participation of the elderly in clinical trials still exist, including provider reluctance to recommend trials due to toxicity fears, limited expectation of benefit, or simply ageism (Carreca & Balducci, 2009). Patients may be reluctant to participate in clinical trials for similar reasons, as well as concern for the cost of participation and the strain on caregivers. Limited representation of older adults in clinical trials impedes the development of evidence-based practice guidelines specific to this population (Lichtman et al., 2007). Familiarity with recent clinical trial data, including risk-adapted treatment guidelines and the complex attributes of the older adult, will provide the advanced practitioner with sound clinical management strategies and will effectively eliminate chronologic age as a sole barrier to treatment of common hematologic malignancies.

Geriatric Oncology: Unique Needs of the Older Adult with Cancer

The concept of geriatric oncology was first recognized in a symposium organized in 1983 by Dr. Rosemary Yanick and co-sponsored by the National Cancer Institute and the National Institute on Aging, which resulted in a monograph entitled "Perspectives on Prevention and Treatment

of Cancer in the Elderly" (Yanick, 1997). Today, the International Society of Geriatric Oncology exists, and the National Comprehensive Cancer Network (NCCN) has developed clinical practice guidelines for Senior Adult Oncology (NCCN, 2010). In addition, numerous publications that evaluate specific attributes of the older adult with cancer have emerged.

All of these initiatives recognize that chronologic age alone is a poor predictor of outcome. Instead, concepts well established in gerontology, such as functional independence or impairment, and assessment tools, such as the multidimensional comprehensive geriatric assessment (CGA) tool, have been integrated into the management of the oncology patient. The CGA incorporates elements evaluating functional status, physical performance, cognitive ability, psychological status, medication review, and social support (NCCN, 2010).

More recently, the concept of a comorbidity index has emerged as an adjunct to well-established prognostic scoring systems, which focus primarily on specific disease characteristics such as morphology, cytogenetics, and molecular indices. The terms "fit," "unfit," and "frailty" have been used to describe older patients and guide treatment (Kumar, Katheria, & Hurria, 2010; Wedding, Honecker, Boekemeyer, Pientka, & Hoffken, 2007). Age-related physiologic changes in organ function, drug metabolism, and predisposition to adverse events have also been described (Table 3). Nutritional status is an independent predictor of disability and mortality in older adults (Given & Given, 2008). Clearly, aging is a heterogeneous process. Tools that allow individualized risk analysis beyond chronologic age are critical to effective treatment of the older adult with a hematologic malignancy.

Functional Status, Frailty, and Comorbidity

The current standard for the evaluation of functional status for patients enrolled in clinical trials is either the Eastern Cooperative Oncology Group (ECOG) performance status (PS) or the Karnofsky PS (KPS) focusing on activities of daily living (ADLs) and instrumental ADLs (IADLs). ADLs include the ability to bathe, dress, toilet, maintain continence, transfer, and eat independently (Balducci & Extermann, 2000). IADLs include activities such as maintaining finances,

Table 2. High-risk features for common hematologic malignancies in the elderly

Disease	High-risk features
AML	High-risk cytogenetics: Complex cytogenetics (> 5 abnormalities) Abnormalities of chromosome 5 or 7 17p abnormality, t(6;9), t(3;21), 11q23 deletion (common in MDR AML) Intermediate cytogenetic risk: +8, +6, +21, –Y, 12p– *NPM1* mutation with *FLT3*-ITD *CEBPα* mutation Increasing blasts Antecedent hematologic malignancies
ALL	*BCR-ABL*–positive disease Undifferentiated leukemia Age > 35 years WBC count > 30×10^9/L at diagnosis Null ALL CD10+ (CALLA) mature B-cell ALL More than 4–5 weeks to achieve a CR (> 0.1% residual disease by PCR)
MDS	High-risk cytogenetics: Complex (> 3 abnormalities) Chromosome 7 abnormalities (7q, –7, del7p); t(5q) Inversion 16, t(8;12)—implies diagnosis of AML Thrombocytopenia at presentation High-transfusion burden IPSS intermediate-2 high-risk disease
NHL	Elevated lactase dehydrogenase IPI stage III–IV disease High Ki-67 rate Elevated HLA-DR Elevated c-Myc (> 80%) Bcl-2 overexpression
CLL	High-risk cytogenetics: del(11q) and del(17p) Intermediate-risk cytogenetics: 14q, 12+ Umutated (germline) IgVH gene CD38 expression in > 30% of lymphocytes ZAP-70 expression in > 20% of lymphocytes Elevated serum thymidine kinase Presence of large cell transformation Elevated β2 microglobulin Doubling time of lymphocyte count < 12 months Rai stage 3 or 4, Binet stage C
MM	High-risk cytogenetics: t(4;14), t(14;16), –17p13, –13q Serum albumin < 3 g/dL Plasma cell labeling index > 3% Hypoploidy ISS stage III Bone marrow plasma cells >50% β2 microglobulin > 4 mg/L Creatinine > 2 mg/dL Platelet count < 150,000/mm^3 Relapse < 12 months from HSCT or first-line therapy

Note: AML = acute myelogenous leukemia; ALL = acute lymphoblastic leukemia; MDS = myelodysplastic syndromes; NHL = non-Hodgkin's lymphoma; CLL = chronic lymphocytic leukemia; MM = multiple myeloma; MDR = multidrug resistance; ITD = internal tandem duplications; WBC = white blood cell; CR = complete response; PCR = polymerase chain reaction; IPSS = International Prognostic Scoring System; IPI = International Prognostic Index; ISS = International Staging System; HSCT = hematopoietic stem-cell transplantation. From Foon & Halleck, 2009; International Myeloma Workshop, 2009; Kurtin, 2010; Farag et al., 2006; Dohner et al., 2010.

Table 3. Age-related physiologic changes on pharmacokinetics and clinical significance

Organ/function	Age-related changes	Clinical significance
Bone marrow	Decreased red blood cell mass Hematopoietic senescence	Increased risk for myelosuppression and secondary effects Prolonged recovery
Cardiovascular	Increased incidence of cardiovascular comorbidities (congestive heart failure, hypertension)	Increased risk of acute cardiomyopathy Baseline and periodic evaluation of ejection fraction is required
Gastrointestinal	Decreased gastric motility and secretion Decreased absorptive surface	Increased risk of drug-drug reactions Increased risk of reactions to oral compounds
Hepatic	Reduced drug metabolism Reduced activity of cytochrome p450 pathways Decreased splanchnic circulation	Increased risk of drug reactions Increased risk of hepatotoxicity Increased risk of drug toxicity for drugs with hepatic metabolism/clearance
Neurologic	Age-related changes in white matter Reduced sensory perception	Increased risk of central and peripheral neuropathy
Renal	Reduced glomerular filtration rate Reduced tubular reabsorption—loss of active nephrons	Increased risk for drug toxicity for drugs with renal excretion Requires careful evaluation of creatinine clearance and dose modification to reduce toxicity
Musculoskeletal	Decreased muscle mass	Shift in distribution of drugs
General	Increase in body fat, decrease in muscle mass, reduction of total body water	Shift in distribution of fat-soluble compounds
Nutritional	Protein calorie malnutrition	Altered distribution of drugs Decreased tolerance to chemotherapy Delayed wound healing
Age-related disease attributes	Increased prevalence of multiple drug resistance (MDR-1) phenotype	Resistance to therapy for acute myelogenous leukemia
	Increased resistance to apoptosis	Associated with follicular lymphoma and resistance to selected treatments
	Increased adhesion of neoplastic cells to the bone marrow stroma	Associated with multiple myeloma

Note: Based on Balducci et al., 2009; Carreca & Balducci, 2009; NCCN, 2010; and Wedding et al., 2007.

shopping, housekeeping, transportation, and self-medication (Balducci & Extermann, 2000).

The difficulty of evaluating a patient in his or her home environment during normal daily routines limits the accuracy of KPS or ECOG PS scores. Health care providers often estimate PS based on patient and family descriptions or a "hunch" that the patient is overstating his or her independence. Furthermore, these systems offer limited estimation of functional decline, morbidity, and mortality in the presence of active treatment (Saif & Lichtman, 2009).

Oncology-specific evaluation of the "fit" or "unfit" adult is also limited. The concept of frailty has been the focus of other groups or studies, including the American Medical Association, the Cardiovascular Health Study (CHS), the Women's Health and Aging Studies, and the Canadian Study of Health and Aging. Frailty is described differently by each group, though the varied descriptions include similar concepts such as weight loss, weakness, poor nutritional intake, cognitive impairment, and poor endurance (Kumar et al., 2010). The CHS evaluated 5,317 patients using frailty criteria (shrinking, weakness, poor endurance, poor energy, slowness, and low physical activity) and found frailty to be associated with hospitalization, falls, declining ADLs (including diminished mobility), and death ($p <$ .001 for all; Chaves, Kuller, O'Leary, Manolio, & Newman, 2004).

These tools have been applied to selected oncology populations, with similar findings of increased vulnerability in frail patients (Saif & Li-

chtman, 2009). Studies specific to patients with hematologic malignancies are limited. The NCCN guidelines for Senior Adult Oncology (NCCN, 2010) suggest evaluation of the older adult using the CGA with four primary categories and suggested treatment approaches (Table 4). However, the CGA is time-consuming and would be difficult to incorporate in most busy oncology practices (Given & Given, 2008).

Table 4. Clinical approaches to the older adult with cancer

Patient characteristics	Approach to treatment
Functionally independent without comorbidities	Candidates for most forms of therapy with consideration of goals of treatment/expected outcomes
Intermediate functional impairment unable to tolerate intensive life-prolonging curative therapy	Application of individualized pharmacologic approach
Major functional impairments or complex comorbidities	Candidates for palliative therapies only
Poor prognosis and limited functional status	Symptom management and supportive care

Note: Based on information from NCCN, 2010; Saif & Lichtman, 2009.

Older adults commonly have multiple medical comorbidities, including cancer, which require ongoing evaluation and management, multiple medications, and often multiple health care providers. As a result, older adults are prone to drug-drug interactions and are at increased risk of morbidity and mortality from any of their illnesses. Evaluation of medical problems using a comorbidity index score was found to be an independent prognostic factor for patients with cancer (Piccirillo, Tierney, Costas, Grove, & Spitznagel, 2004). Most early studies evaluated patients with solid tumors. Several recent publications specific to patients with hematologic malignancies have confirmed the importance of comorbidity evaluation in guiding treatment selection. Selected studies will be highlighted in the following paragraphs.

Disease-Specific Risk Analysis for Hematologic Malignancies

DLBCL

The addition of rituximab (Rituxan) to cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy has resulted in a 5-year OS rate of 41% for patients > 60 years of age with diffuse large B-cell lymphoma (DLBCL; Sehn et al., 2005). Elderly individuals represent the majority of patients with DLBCL. Hershman et al. (2008) evaluated 9,438 patients over the age of 65 diagnosed with DLBCL from 1991–2002. Only 42% of these patients (4,001) received doxorubicin-based chemotherapy, such as CHOP. Doxorubicin use was associated with a 29% increase in the risk of congestive heart failure (CHF). Other risk factors for CHF included increasing age, cumulative doses of doxorubicin, any comorbidity, diabetes, and hypertension. However, only hypertension intensified the effect of doxorubicin with respect to CHF risk (hazard ratio [HR] = 1.8; $p < .01$). In the 8 years after diagnosis, the adjusted CHF-free survival rate was 74% in the doxorubicin-treated patients versus 79% in patients not treated with doxorubicin. Many patients were not offered doxorubicin based solely on age.

Given the increased incidence of NHL in older patients and the key role of CHOP chemotherapy in improving survival for elderly patients with DLBCL, the authors suggested that the survival effect of CHOP treatment may outweigh the risk of cardiotoxicity (Hershman et al., 2008). Careful pretreatment screening (including a complete physical assessment, aggressive concurrent management of hypertension and other comorbidities, administration of cardioprotective agents when appropriate, and continued surveillance during treatment) may provide more effective therapy in elderly patients.

In a phase II study, Tirelli et al. (2009) investigated the feasibility of a CGA-driven treatment selection for elderly patients with newly diagnosed DLBCL. The authors stratified 100 patients by comorbidities and PS. Patients without comorbidities received standard R-CHOP, patients with mild cardiomyopathy received epirubicin instead of doxorubicin, and patients with underlying cardiomyopathy did not receive an anthracycline. Patients with diabetes did not receive prednisone, and patients with pre-existing neuropathy did not receive vincristine. Dosing was modified according to patients' ADL/IADL scores, with a 25% dose reduction for an intermediate score and

a 50% dose reduction for a poor score. Complete responses were achieved in 81%, with a 20% relapse rate at 5 years. The 5-year OS, disease-free survival (DFS), and event-free survival (EFS) were 58%, 78%, and 50% respectively. This study provides an interesting approach to individualized treatment based on disease and patient-specific characteristics, with the goal of offering curative therapy to all patients but avoiding overtreating patients with severe comorbidities.

In 2009, Delarue et al. presented data from a planned interim analysis of a phase III open-label randomized trial (GELA study LNH03-6B) evaluating the efficacy of R-CHOP given every 14 days (R-CHOP 14) compared with R-CHOP given every 21 days (R-CHOP 21) in 201 patients between the ages of 60 and 80 years (median age, 72 years). In the R-CHOP 14 cohort, 90% of the patients received granulocyte colony-stimulating factor (G-CSF), versus only 66% of patients in the R-CHOP 21 cohort. Grade 3/4 hematologic toxicities, red blood cell and platelet transfusions, febrile neutropenia, and hospitalizations for adverse events were more common in the R-CHOP 14 cohort. Based on this interim analysis, the authors favored R-CHOP 21 as the best choice for elderly patients with DLBCL.

CLL

Foon and Halleck (2009) provided a comprehensive review of recent trials, publications, conference proceedings, and trial registers pertaining to CLL. In this review, the authors described the changing treatment paradigm for CLL, with a shift toward tailored treatment. Included in this approach is consideration of stage of disease, patient "fitness" (including comorbidity), and molecular cytogenetics. Chronologic age is not included in the risk stratification. Therefore, a "fit" elderly patient with early-stage disease and no evidence of the deletion of chromosome 17p (del[17p]), an unfavorable cytogenetic finding, would be considered for more aggressive therapy such as FCR (fludarabine, cyclophosphamide, and rituximab) to induce an early complete molecular response, increasing the probability of a durable response. However, this regimen is associated with increased incidences of grade 3/4 neutropenia (52%–89%) and grade 3/4 thrombocytopenia (78%), important considerations in treating an older patient.

An alternative regimen, known as FCR-lite (dose-reduced fludarabine and cyclophosphamide) was studied to evaluate its efficacy and safety in 50 previously untreated patients with CLL (Foon & Halleck, 2009). All 50 patients responded (ORR = 100%), with complete responses (CR) documented in 79%. All patients achieving a CR (with the exception of one patient who died of a myocardial infarction while still in remission) remained in a CR at a median follow-up of 2.4 years. Importantly, the incidence of grade 3/4 neutropenia was 13%. Patients with del(17p) have a poor outcome with standard chemoimmunotherapy. Patients within the age parameters for hematopoietic stem-cell transplant (HSCT) who have the del(17p) would be considered for alemtuzumab (Campath) with rituximab, followed by a nonmyeloablative, allogeneic stem-cell transplant.

HSCT

Sorror et al. (2008) evaluated 341 patients enrolled in the Fred Hutchinson Cancer Research Center (Seattle, WA) consortium studies for HSCT. The records were reviewed using the KPS and the Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI; Table 5), a 17-item tool adapted from the Charlson Comorbidity Index, which has been used primarily in patients with solid tumors. The HCT-CI includes definitions for 17 common comorbidities, inclusive of those common in patients with hematologic malignancies, with each assigned a weighted score of 1–3 (Sorror et al., 2005). All major hematologic diseases were included in this evaluation; AML (23%), NHL (19%), MM (18%), MDS (10%), and CLL (10%) were the most common. The median age of patients in this study was 56 years, and the oldest patient was 74 years.

Higher HCT-CI scores were associated with higher incidences of grade 3 ($p = .001$) and grade 4 ($p = .004$) toxicities, nonrelapse-related mortality ($p < .0001$), and overall mortality ($p = .0002$). The authors generated a consolidated HCT-CI and KPS score and stratified patients into four risk groups with 2-year survivals of 68% (HCT-CI, 0–2; KPS > 80%), 58% (HCT-CI, 0–2; KPS < 80%), 41% (HCT-CI, ≥ 3; KPS > 80%) and 32% (HCT-CI ≥ 3; KPS < 80%). Patients with the best performance status and the fewest comorbid conditions experienced fewer grade 3/4 adverse events

Table 5. Definitions and weighted scores for the HCT-CI

Comorbidity	Definition	Weight
Arrhythmia	Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmia	1
Cardiac	Coronary artery disease, congestive heart failure, myocardial infarction, or ejection fraction < 60%	1
Inflammatory bowel disease	Chronic disease or ulcerative colitis	1
Cerebrovascular disease	Transient ischemic attacks or cerebrovascular accident	1
Psychiatric disturbance	Depression or anxiety requiring psychiatric consult or treatment	1
Hepatic, mild	Chronic hepatitis, bilirubin > ULN to 1.5× ULN, or AST/ALT > ULN to 2.5× ULN	1
Obesity	Body mass index > 35 kg/m^2	1
Infection	Requiring antimicrobial treatment after day 9	1
Rheumatologic	Systemic lupus erythematosus, rheumatoid arthritis, polymyositis, mixed connective tissue disease, polymyalgia rheumatica	2
Peptic ulcer	Requiring treatment	2
Renal, moderate/severe	Serum creatinine > 2 mg/dL, on dialysis, or prior renal transplantation	2
Pulmonary, moderate	DLCO and/or FEV_1 66%–80% or dyspnea on slight activity	2
Prior solid tumor	Treated at any time, excluding nonmelanoma skin cancer	3
Heart valve disease	Except mitral valve prolapse	3
Pulmonary, severe	DLCO and/or FEV_1 < 66% or dyspnea at rest or requiring oxygen	3
Hepatic, moderate/severe	Liver cirrhosis, bilirubin > 1.5× ULN or AST/ALT > 2.5× ULN	3

Note: HCT-CI = Hematopoietic Cell Transplantation Comorbidity Index; ULN = upper limit of normal; AST = aspartate transaminase; ALT = alanine transaminase; DLCO = diffusion capacity for carbon monoxide; FEV_1 = forced expiratory volume in one second. Adapted from Sorror et al., 2005; Sorror et al., 2008.

and improved survival in this study (Sorror et al., 2008). These principles are often applied intuitively in clinical practice; however, the value of an objective, scientifically tested tool cannot be overstated.

AML

Similarly, HCT-CI scores have been shown to be predictive of prognosis in patients > 60 years receiving induction therapy for AML. Elderly patients with AML who have a poor prognosis are more likely to exhibit therapeutic resistance and suffer treatment-related early death (Dohner et al., 2010). Etienne and colleagues (2007) applied the HCT-CI in a retrospective analysis of 133 patients aged ≥ 70 years when treated for AML between 1995–2004. Adverse prognostic factors included an unfavorable karyotype (i.e., del[5q], del[7q], 11q23 rearrangements, complex karyotype), leukocytosis ≥ 30 g/L, CD34 expression on leukemic cells, and an HCT-CI score > 1. The risk of early mortality (p = .02) and decreased survival (p = .01) was increased in the patients with an HCT-CI score > 1.

The Swedish Acute Leukemia Registry (Juliusson et al., 2009) evaluated prognostic factors in 2,767 elderly patients with AML diagnosed between 1997–2005. The median age was 72 years, with the peak incidence of AML in ages 80–85. PS was evaluated using the ECOG score. Early death rates (within 30 days of diagnosis) were dependent on both age and PS; however, early death rates were lower in older patients (76–89 years) treated with intensive therapy (ECOG PS 0–II = 14% v. ECOG PS III–IV = 36%) compared with patients who were offered only palliative therapy (ECOG PS 0–II = 17% v. ECOG III–IV = 52%). Early death rates were higher in all age groups with poor PS; however, some patients who received intensive therapy were included in the long-term survivor group. Although PS is more predictive for early death than age, ECOG PS alone should not exclude the option of intensive therapy for all patients. Cytogenetics and comorbidities were not evaluated in this study.

An international expert panel on AML has recently published updated evidence-based and

expert opinion-based recommendations for the diagnosis and treatment of AML (Dohner et al., 2010). The panel recommended that all AML patients should undergo a comprehensive disease evaluation, including cytogenetics, which has established diagnostic and prognostic values. Evaluation of newer molecular markers (NPM1, CEBPA, FLT3) is encouraged, with growing evidence for prognostic value and treatment selection. Recommendations specific to the older adult include subdividing older patients into two groups, ages 60–74 and 75 years and older, based on a number of studies, indicating that advanced age is associated with poor outcomes. Several factors associated with advanced age are suspected to contribute to poor outcomes, including PS, comorbidities, and age-dependent changes in disease (adverse cytogenetics, MDR phenotype, antecedent hematologic malignancies). However, the panel emphasized that intensive treatment should not be withheld based on age alone, as intensive treatment has been shown to improve quality of life and prolong survival compared with supportive care alone (Dohner et al., 2010).

Sekeres and colleagues (2009) evaluated 1,313 patients with newly diagnosed AML (median age = 60 years). Interestingly, as seen in multivariate analysis, delaying induction therapy up to 5 days was associated with reduced CR and OR rates in younger patients ($p < .001$) but not in older patients ($p < .19$). Therefore, it may be feasible to wait for critical diagnostic results and a complete evaluation of comorbidities and social support resources before initiating induction therapy for patients with AML, allowing for an individualized approach.

A cost-burden analysis of 6,981 patients with AML over the age of 65 found 30% of the patients (2,094) received induction chemotherapy, with only 38% of those achieving a CR (Cohen, Davidson, Scharf, & Middlebrook, 2009). Using the Medicare component of the consumer price index, costs for treatment of AML in this age group for the first two years after diagnosis (all settings) were calculated according to a budget-impact model. A patient with AML undergoing chemotherapy incurred costs of $120,468 over 2 years, whereas a patient not receiving chemotherapy incurred costs of $40,720. Refinement of the diagnostic and prognostic models for treatment selection in older patients with AML is necessary to select patients who are more likely to respond to standard induction therapy. Combining disease-specific characteristics with patient-specific attributes, including PS and comorbidity, will be necessary to select the most appropriate treatment for each patient. Refinement of toxicity management and effective resource utilization during treatment may also provide cost savings without compromising treatment outcomes.

MM

One of the primary questions in the current approach to treatment selection for patients with newly diagnosed MM is whether they are eligible for transplant (NCCN, 2010). Autologous transplantation is the preferred choice and is much better tolerated than allogeneic HSCT. However, patients who are older and have comorbidities are not believed to be good candidates. Therefore, alternative standard therapies are required for effective treatment of this population.

Long-term follow-up on OS from two large, phase III, randomized clinical trials (MM-090, MM-010) confirmed superior CR, time to progression (TTP), and duration of response for lenalidomide (Revlimid) combined with dexamethasone (Len/Dex) versus dexamethasone (Dex) alone in relapsed, refractory MM (Dimopoulos, et al., 2009). A subsequent retrospective analysis identified 285 of the 704 patients enrolled in those trials as elderly (age > 65 years) and found similar benefit in the older population, with improved ORR (58.9% v. 20.9%) and median TTP (60 v. 20 weeks) favoring Len/Dex, and OS (79 weeks in the Dex cohort and not yet reached in the Len/Dex cohort [$p < 0.001$]) all favoring Len/Dex (Chanan-Khan et al., 2009).

Treatments that are feasible in the older adult or other transplant-ineligible patients will be critical to the effective treatment of MM. Bortezomib (Velcade), a proteasome inhibitor, has shown efficacy and safety in the treatment of patients with MM (NCCN, 2010). However, peripheral neuropathy (PN) has been reported as a dose-limiting toxicity of this treatment. Gay et al. (2009) evaluated the incidence of PN in 511 elderly patients (age > 65 years) randomized to receive a combination of bortezomib, melphalan, prednisone, and thalidomide (VMPT) or bortezomib, melphalan, and prednisone (VMP). The protocol was amended after the first 141 patients, chang-

ing the bortezomib dose to 1.3 mg/m^2 weekly for 2 consecutive weeks from 1.3 mg/m^2 twice weekly for 2 consecutive weeks every 21 days.

In multivariate analysis, the only predictive factor for a lower incidence of PN was the weekly dose bortezomib ($p < .0001$). Additionally, the weekly administration of bortezomib significantly lowered dose reductions ($p = .001$) or discontinuations ($p < .001$) and did not adversely affect 2-year PFS. OS was reduced slightly ($p = .44$). The addition of thalidomide, also known to be associated with PN, did not increase the incidence of grade 3/4 PN in this population of older adults. Dose-limiting adverse events curb the efficacy of treatment, including novel therapies, and often reduce patients' quality of life. This trial demonstrates the value of taking an effective therapy and refining it so that its efficacy is not compromised, making treatment feasible in the older patient with MM.

MDS

MDS represents a group of heterogeneous myeloid stem-cell disorders. The peak incidence of this syndrome is in the 7th and 8th decades of life. Cytopenias, in particular anemia that requires chronic transfusions, are the most common findings in these diseases. The only potential curative therapy in these syndromes is an allogeneic HSCT. Due to the advanced age of this population and the low probability of a healthy living sibling donor, the required matched, unrelated HSCT is not feasible for the majority of patients.

The first active therapy approved by the U.S. Food and Drug Administration for MDS was azacitidine (Vidaza; Celgene Corp., 2009a). Remarkably, within 5 years of its approval, azacitadine has been shown to have a survival advantage when compared with three commonly used approaches for treatment of high-risk MDS, including standard leukemia induction therapy, low-dose cytarabine, or best supportive care (Fenaux et al., 2009).

Two additional active compounds, lenalidomide (Celgene Corp., 2009b) and decitabine (Dacogen; Eisai Inc., 2008) were approved in 2005 and 2006, respectively, and have also shown benefit in disease response, including hematologic improvements and transfusion independence. No survival benefit has been noted to date in reported trials for either lenalidomide or decitabine, and each of these treatments is associated with potential adverse events (Kurtin, 2010).

A review of 500 consecutive MDS patients at The University of Texas M. D. Anderson Cancer Center (Houston, TX) from January 2002–June 2004 evaluated comorbidities using the Adult Comorbidity Evaluation-27 (ACE-27), a 27-item evaluation tool developed to assess comorbidities in cancer patients (Naqvi et al., 2009). Follow-up lasted for a median duration of 23.5 months. The median age was 66.6 years, and the population was split evenly between low-risk (International Prognostic Scoring System [IPSS] low/intermediate-1 = 49%) and high-risk patients (intermediate-2/high-risk = 51%). Median survival for the low-risk patients was 40.9 months, compared with 8.1 months in the high-risk population. Survival for patients with severe comorbidities (14.6%) was 9.7 months, compared with those with moderate comorbidities (21.6%) at 15.2 months and mild comorbidities (42.6%) at 18.9 months ($p < .0001$). In total, 44 patients with mild-to-moderate comorbidities underwent HSCT, and 47.7% of those patients died, emphasizing the difficulty of this treatment approach in the older adult. Importantly, this patient population was evaluated prior to the availability of active therapies for MDS; still, it demonstrates the significance of comorbidities in the treatment outcomes and survival of patients with MDS.

MDS is most common in older adults with a higher incidence of nonhematologic comorbidities. A study of 1,344 MDS patients conducted by Della Porta et al. (2008) found the incidence of nonhematologic comorbidities to be 54%, with cardiac disease as the most common (25%) and the leading cause of nonleukemic death (NLD). The onset of a comorbidity significantly affected the risk of NLD (HR, 4.31; $p < .001$), cardiac disease (HR, 4.16), and death (HR, 4.88; $p < .001$ for both). Serum ferritin levels in this group were significantly related to the risk of cardiac disease and death ($p = .001$). The onset of cardiac, liver, renal, and pulmonary diseases and solid tumors was found to independently affect the risk of NLD. Complete evaluation of comorbidities, initiation of active therapies for MDS to minimize transfusion burden, and interventions for iron overload may reduce the incidence of NLD.

Each of the aforementioned studies illustrates the continued refinement of prognostic evaluation beyond disease-specific characteristics. The ability to risk-stratify older patients based on physiologic and sociologic measures such as co-

morbidities, functional status, support systems, and goal of treatment will promote an individualized approach to treatment selection. Further development of evaluation tools specific to patients with hematologic malignancies will be needed. Familiarity with the current research specific to hematologic malignancies and more general guidelines, such as the NCCN guidelines for Senior Adult Oncology, will assist the advanced practitioner in counseling patients who are considering treatment options as well as identifying patients at high risk for adverse events.

Social Support

Management of hematologic diseases is primarily an outpatient process. Avoidance of hospitalization is a primary goal due to the associated risk and costs. Outpatient management, however, places a significant burden on patients and their support systems. The presence of a reliable caregiver, proximity to the treatment center, availability of other necessary support services, and reliable transportation are all necessary for the effective management of the older adult. Collaboration and communication with the patient's network of health care providers may promote improved management of comorbidities.

Functional decline is associated with a loss of independence and decreased quality of life (Carreca & Balducci, 2009). Most of the hematologic diseases are not curable; therefore, the preservation of quality of life and independent function should remain a priority. Careful consideration of the patient- and disease-related factors together with the expectations of the patient and the consistent availability of caregivers is necessary to make the patient better, whatever the outcome of treatment.

Summary

Recent clinical advances in the diagnosis, prognostication, and treatment of hematologic diseases have improved response rates and survival for common hematologic malignancies. Additional consideration for age-related physiologic changes, comorbidities, and social and financial support is necessary to safely treat the older adult. Collaboration with colleagues in social services, nutritional sciences, and finance will promote more effective evaluation of the needs of the older patient. Development of comorbidity and functional assessment tools specific to hematologic malignancies is needed both to identify patients who may benefit from aggressive therapy and to protect those who may require less intensive therapy due to an increased risk of morbidity and mortality.

Collaboration with health care providers in other disease specialties, including cardiology, nephrology, neurology, palliative care, gerontology, and internal medicine, will promote familiarity with current approaches to treatment of common comorbid conditions in the elderly. An individualized approach to treatment, inclusive of, but not being confined by, treatment guidelines, will promote quality of life and optimal treatment outcomes. Advanced practitioners are in a unique position to promote favorable outcomes for the older adult with a hematologic malignancy by conducting a comprehensive yet individualized assessment, using current research and guidelines as well as facilitating a collaborative approach to management.

REFERENCES

Balducci, L., Colloca, G., Cesari, M., Gambassi, G. (2009). Assessment and treatment of elderly patients with cancer. *Surgical Oncology.* doi:10.1016/j.suronc.2009.11.008

Balducci, L., & Extermann, M. (2000). Management of cancer in the older person: a practical approach. *Oncologist, 5,* 224–237.

Carreca, I., & Balducci, L. (2009). Cancer chemotherapy in the older patient. *Urologic Oncology: Seminars and Original Investigation, 27,* 633–642.

Celgene Corp. (2009a). Vidaza® (azacitidine) prescribing information. Retrieved from http://www.vidaza.com/pdf/PI_FINAL.pdf

Celgene Corp. (2009b). Revlimid® (lenalidomide) prescribing information. Retrieved from http://www.revlimid.com/pdf/REVLIMID_PI.pdf

Chanan-Khan, A., Weber, D., Chaves, P., Kuller, L., O'Leary, D., Manolio, T., & Newman, A. (2004). Subclinical cardiovascular disease in older adults: Insights from the Cardiovascular Health Study. *The American Journal of Geriatric Cardiology, 13,* 137–149.

Chanan-Khan, A. A., Weber, D., Dimopoulos, M. A., Chen, C., Niesvizky, R., Wang, M.,...Knight, R. (2009). Lenalidomide (L) in combination with dexamethasone (D) improves survival and time to progression in elderly patients with relapsed or refractory multiple myeloma. *Blood, 114,* abstract 3551.

Chaves, P. H., Kuller, L. H., O'Leary, D. H., Manolio, T. A., & Newman, A. B.; Cardiovascular Health Study. (2004). Subclinical cardiovascular disease in older adults: insights from the Cardiovascular Health Study. *American Journal of Geriatric Cardiology, 13,* 137–151.

Cohen, A., Davidson, N., Scharf, J., Middlebrook, D. (2009). Cost burden analysis of ineffective induction chemotherapy in elderly patients with AML. *Blood, 114,* abstract 4531.

Delarue, R., Tilly, H., Salles, G., Gisselbrecht, C., Mounier, N., Fournier, M., ... Bosly, A. (2009). R-CHOP14 compared to R-CHOP21 in elderly patients with diffuse large B-cell lymphoma: Results of the interim analysis of the

LNH03-6B GELA Study. *Blood, 114,* abstract 406.
Della Porta, M. G., Kuendgen, A., Malcovati, L., Zipperer, E., Pascutto, C., & Travaglino, E. (2008). Myelodysplastic syndrome (MDS)-specific comorbidity index for predicting the impact of extra-hematologic comorbidities on survival of patients with MDS. *Blood, 12,* abstract 2677.
Dimopoulos, M. A., Chen, C., Spencer, A., Niesvizky, R., Attal, M., Stadtmauer, E. A.,...Weber, D. M. (2009). Long-term follow-up on survival from the MM-009 and MM-010 phase III trials of lenalidomide plus dexamethasone in patients with relapsed or refractory multiple myeloma. *Leukemia, 23,* 2147–2152.
Dohner, H., Estey, E., Amadori, S., Applebaum, F., Buchner, T., Burnett, A.,...Lowenberg, B. (2010). Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. *Blood, 115,* 453–474.
Eisai Inc. (2008). Dacogen® (decitabine) prescribing information. Retrieved at http://www.dacogen.com/hcp/LinkedFiles/Prescribing_Information.pdf
Etienne, A., Esterni, B., Charbonnier, A., Mozziconzcci, M. J., Arnoulet, C., Coso, D.,...Vey, N. (2007). Comorbidity is an independent predictor of complete remission in elderly patients receiving induction chemotherapy for acute myeloid leukemia. *Cancer, 109,* 1376–1383.
Farag, S., Archer, K., Mrozek, K., Ruppert, A., Carroll, A., Vardiman, J.,...Bloomfield, C. D. (2006). Pre-treatment cytogenetics add to other prognostic factors predicting complete remission and long-term outcome in patients 60 years of age or older with acute myeloid leukemia: results from Cancer and Leukemia Group B 8461. *Blood, 108,* 63–73.
Fenaux, P., Mufti, G. J., Hellstrom-Lindberg, E., Santini, V., Finelli, C., & Giagounidis, A. (2009). Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: A randomised, open-label, phase III study. *Lancet Oncology, 10,* 223–232.
Foon, K. A., & Halleck, M. J. (2009). Changing paradigms in the treatment of chronic lymphocytic leukemia. *Leukemia*. doi:10.1038/leu.2009.266.
Gay, F., Bringhne, S., Genuardi, M., Ross, D., Ria, R., Romano, A., ... Palumbo, A. (2009). The weekly infusion of bortezomib reduces peripheral neuropathy. *Blood, 114,* abstract 3887.
Given, B., & Given, C. (2008). Older adults and cancer treatment. *Cancer, 113(12 suppl),* 3505–3511.
Hershman, D., McBride, R., Eisenberger, A., Tsai, W., Grann, V., & Jacobson, J. (2008). Doxorubicin, cardiac risk factors, and cardiac toxicity in elderly patients with diffuse B-cell non-Hodgkin's lymphoma. *Journal of Clinical Oncology, 26,* 3159–3165.
International Myeloma Workshop. (2009) Guidelines for risk stratification in multiple myeloma. Report from the 2008 International Myeloma Workshop Consensus Panel 2. Retrieved from http://www.mw-delhi09.com/spargoDocs/Consensuspaneltwo.pdf
Jemal, A., Siegel, R., Ward, E., Hao, Y., Xu, J., & Thun, M. J. (2009). Cancer statistics 2009. *CA Cancer J Clin, 59,* 225–229.
Juliusson, G., Antunovic, P., Derolf, A., Lehman, S., Moligard, L., Stockelberg, D., ... Hoglund, M. (2009). Age and acute myeloid leukemia: Real world data on decision to treat and outcomes from the Swedish Acute Leukemia Registry. *Blood, 113,* 4179–4187.
Kumar, S., Katheria, V., Hurria, A. (2010). Evaluating the older adult with cancer: Understanding frailty and the geriatric assessment. *CA Cancer J Clin*. doi:10.3322/caac.20059.
Kurtin, S. (2010). Leukemia and myelodysplastic syndromes. In Yarbro, C. H., Wujcik, D., & Gobel, B. H. (Eds.), *Cancer Nursing: Principles and Practice, Seventh Edition*. Sudbury, MA: Jones and Bartlett Publishers, LLC.
Lichtman, S. M., Balducci, L., & Aapro, M. (2007). Geriatric oncology: A field coming of age. *Journal of Clinical Oncology, 25,* 1821–1823.
Lichtman, S. M., Wildiers, H., Chatelut, E., Steer, C., Budman, D., Morrison, V. A.,...Aapro, M.; International Society of Geriatric Oncology Chemotherapy Taskforce. (2005). Evaluation of chemotherapy in older patients–an analysis of the medical literature. *Journal of Clinical Oncology, 25,* 1832–1843.
Naqvi, K., Garcia-Manero, G., Sardesi, S., Oh, J., Pierce, S., Lei, X., & Suarez-Almazor, M. E. (2009). Comorbidities and myelodysplastic syndromes. *Blood, 114,* abstract 2789.
National Comprehensive Cancer Network. (2010). NCCN Clinical Practice Guidelines in Oncology™: Senior Adult Oncology. Retrieved from http://www.nccn.org/professional/physician_gls/PDF/senior.pdf
Piccirillo, J. F., Tierney, R. M., Costas, I., Grove, L. & Spitznagel, E. L. (2004). Prognostic importance of comorbidity in a hospital-based cancer registry. *Journal of the American Medical Association, 291,* 2441–2447.
Saif, M., & Lichtman, S. (2009). Chemotherapy options and outcomes in older adult patients with colorectal cancer. *Critical Reviews in Oncology/Hematology, 72,* 155–169.
Sehn, L., Donaldson, J., Chhanabhai, M., Fitzgerald, C., Gill, K., Klasa, R., ... Connors, J. (2005). Introduction of combined CHOP plus rituximab therapy dramatically improved outcomes of diffuse large B-cell lymphoma in British Columbia. *Journal of Clinical Oncology, 5,* 5027–5033.
Sekeres, M., Elson, P., Kalaycio, M., Advani, A., Copelan, E., Faderl, S.,...Estey, E. (2009). Time from diagnosis to treatment predicts survival in younger, but not older, acute myeloid leukemia patients. *Blood, 113,* 26–36.
Sorror, M., Maris, M. B., Storb, R., Baron, F., Sandmaier, B., Maloney, D., & Storer, B. (2005). Hematopoietic Cell Transplantation (HCT)-Specific Comorbidity Index: A new tool for risk assessment before allogeneic HCT. *Blood, 106,* 2912–2919. doi:10.1182/blood-2005-05-2004
Sorror, M., Storer, B., Sandmaier, B., Maloney, D., Chauncey, T., Langston, A., ... Storb, R. (2008). Hematopoietic Cell Transplantation-Comorbidity Index and Karnofsky Performance Status are independent predictors of morbidity and mortality after allogeneic nonmyeloablative hematopoietic cell transplantation. *Cancer, 112,* 1992–2001.
Talarico, L., Chen, G., & Pazdur, R. (2004). Enrollment of elderly patients in clinical trials for drug registration: A 7-year experience by the U. S. Food and Drug Administration. *Journal of Clinical Oncology, 22,* 4626–4631.
Tirelli, U., Fratino, L., Balzarotti, M., Uziel, L., Giacalone, A., Ferreri, A., ... Spina, M. (2009). Comprehensive geriatric assessment-adapted chemotherpay in elderly patietns (> 70 years) with diffuse large B-cell non-Hodgkin's lyphoma (DLBCL): Final results and long term follow-up. *Blood, 114,* abstract 2684.
U. S. Social Security Administration. (2009). Period life table. Retrieved from: http://www.ssa.gov/OACT/STATS/table4c6.html
Wedding, U., Honecker, F., Boekemeyer, C., Pientka, L., & Hoffken, K. (2007). Tolerance to chemotherapy in elderly patients with cancer. *Cancer Control, 14,* 44–56.
Yanick, R. (1997). Cancer burden in the aged: An epidemiologic and demographic overview. *Cancer, 80,* 1273–1283.