

# Treating the Elderly Patient with Acute Myelogenous Leukemia

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## 1. Introduction

Among patients with acute myeloid leukemia (AML), treatment regimens and outcomes may differ among younger and older adults. Although there is no clear dividing line when considering age in AML, in most studies, "older adults" was defined as over age 60. The management of older patients with AML is a difficult challenge [1]. Older adults are more likely to have comorbidities that can limit treatment options; the disease tends to be more aggressive biologically; and outcomes are worse than in younger patients.

Decisions regarding the optimal treatment of acute myelogenous leukemia in the elderly patient requires the consideration of multiple factors. Population-based studies have demonstrated that, for all age groups, aggressive therapy results in improved survival and quality of life when compared with palliative care. The optimal induction and post remission regimen for older patients has yet to be determined. Furthermore, not all patients are candidates for such therapy. Consideration of patient and disease-related factors can help to determine the appropriateness of intensive therapy in a given patient. For those patients for whom aggressive induction therapy does not seem to be in their best interest, novel agents are being investigated that will hopefully address the issues of induction death and early relapse associated with these patient populations. This topic review will discuss the treatment of older adults with AML.

Most question that must be answer.

1. How Is Acute Myeloid Leukemia in the Elderly Different?
2. What Is the Standard Therapy for the Older Patient With AML?
3. Who Should Not Receive Intensive Therapy?
4. What Treatment Options Are Available for Patients Who Are Not Candidates for Intensive Induction Therapy?

Acute myeloid leukemia (AML) presents at all ages, but is mainly a disease of the elderly, with a median age of 69 years in the white US population[93]. In the Swedish Acute Leukemia Registry, 68% of patients diagnosed with AML since 1973 were over age 60 years; between 1997 and 2005, 75% was aged 60 years or more[94]. Prognosis worsens every decade beginning at age 30 to 40 [93,95]. A report by the German Acute Myeloid Leukemia Cooperative Group looked at patients 16 to 85 years of age enrolled in two consecutive trials

in 1992 and 1999 with no upper age limit who had AML[96]. In a multivariate analysis of prognostic factors, age  $\geq 60$  years was a statistically significant poor prognostic factor for complete remission (CR), overall survival (OS), remission duration, and relapse-free survival (RFS). Population-based studies have reported 3- and 5-year survival rates of only 9% to 10% and 3% to 8%, respectively, in patients over age 60, compared with 5-year survival rates of up to 50% for younger patients[94,96,97]. Poorer outcome has traditionally been considered to be the result of less intensive therapy in this population, concurrent comorbidities, a higher likelihood of underlying hematopoietic disorders, and biologically poor risk disease. Moreover, because of the perception that older adults are less likely to do well with standard therapy, clinicians are less likely to treat these patients aggressively or refer them to centers that do so. As such, lower levels of aggressive treatment may compound underlying prognostic differences associated with patient factors and disease biology.

## 2. Pretreatment evaluation

General – The assessment of an older adult with AML includes those studies used for the pretreatment evaluation of younger adults with AML in addition to more specific investigations of physical functioning, nutrition, and comorbid conditions. Testing specific for older adults is presented in the following sections. The detailed pretreatment evaluation of all patients with AML is presented separately, as is an overview of the comprehensive geriatric assessment of cancer patients.

Physical functioning – The patient's performance status and ability to perform activities of daily living are measures of physical function that can help to predict the ability to withstand rigorous chemotherapy regimens.

Performance status – Several studies have supported the use of the Eastern Cooperative Oncology Group (ECOG) and Karnofsky performance status as measures of physical functioning and prognosis in patients with AML (table-1)

A retrospective study of data from five Southwestern Oncology Group (SWOG) trials that included 968 patients with AML found that the mortality rate within 30 days of initiation of induction therapy is dependent upon both the patient's age and ECOG performance status (PS) at diagnosis.

Thirty-day mortality rates were 2 to 3 percent for patients under the age of 55 years regardless of the PS. For patients over age 55 years, mortality rates ranged from 5 to 18 percent for patients with a PS of zero or 1. Patients 55 to 65 years old with a PS of 2 had a similar mortality rate (18 percent). Patients over age 55 years with a PS of 3 and those over age 65 with a PS of 2 or 3 had much higher mortality rates that ranged from 29 to 82 percent. The proportion of patients with poorer performance status increased with age. PS of 2 or 3 was observed in 15, 24, 26, and 32 percent in those under age 56, 56 to 65, 66 to 75, and >75 years of age, respectively.

Activities of daily living – Geriatricians commonly measure functional status by evaluating basic activities of daily living (ADLs) and instrumental activities of daily living (IADLs). ADLs are the skills that are necessary for basic living, and include feeding, grooming, transferring, and toileting. IADLs are required to live independently in the community and include activities such as shopping, managing finances, housekeeping, preparing meals, and taking medications. Assessment of ADLs and IADLs may add to the functional status obtained from the ECOG or Karnofsky performance status.

## Karnofsky performance scale

Rating	Definition
100 percent	No evidence of disease
90 percent	Normal activity with minor signs of disease
80 percent	Normal activity with effort; signs of disease
70 percent	Cannot do normal activity but cares for self
60 percent	Requires occasional assistance
50 percent	Requires considerable assistance; frequent medical care
40 percent	Disabled, requires special care
30 percent	Severely disabled; hospitalization may be indicated
20 percent	Very sick; hospitalization necessary for supportive treatment
10 percent	Moribund
0 percent	Death

Table 1. Karnofsky performance status scale

Comorbid conditions – Comorbid conditions are poor prognostic factors in older patients with AML [8-10]. Patients with age-related chronic cardiac, pulmonary, hepatic or renal disorders or diabetes suffer greater acute toxicity from chemotherapy.

Older patients may also have decreased bone marrow regenerative capacity, even after successful leukemia cytoreduction. Inability to tolerate long periods of pancytopenia and malnutrition or the nephrotoxicity of drugs such as aminoglycosides or amphotericin remains a major barrier to successful treatment.

Frequently used measures of comorbidity include a modified Charlson comorbidity index (CCI) and the hematopoietic cell transplantation-specific comorbidity index (HCT-CI), neither of which was originally designed for older adults with AML.

Other comorbidity scores have incorporated information on infections prior to treatment and antecedent hematologic disorders. Assessment of other patient-related variables (eg, advanced age, performance status, organ function, karyotype, leukocytosis, CD34 expression) with or without a modified comorbidity index may be helpful for predicting such outcomes as attainment of complete remission, early mortality, and overall survival [3,4,11,12].

Charlson comorbidity index – The original Charlson comorbidity index (CCI) was devised as a measure of comorbidities in older adults. A revised version has been developed for use in older adults with AML with mixed results. (table 2).

A retrospective study evaluated the use of this modified CCI in 133 patients age 70 or older who received induction chemotherapy for AML [11]. CCI scores of zero, 1, and more than 1 were seen in 68, 13, and 19 percent of patients, respectively. When compared with those

with a CCI score of 1 or less, patients with a CCI score greater than 1 had a significantly lower rate of obtaining a complete response (35 versus 63 percent) and had a nonsignificant trend towards higher eight-week mortality rates (30 versus 19 percent) and lower two-year overall survival (24 versus 30 percent).

Modified Charlson comorbidity index

Comorbid condition	Point
Myocardial infarction	1
Heart failure	1
Cerebrovascular disease	1
Ulcer	1
Hepatic disease (mild)	1
Diabetes (mild or moderate)	1
Pulmonary disease (moderate or severe)	1
Connective tissue disease	1
Diabetes (severe with end-organ damage)	2
Renal disease (moderate or severe)	2
Solid tumor (without metastases)	2
Hepatic disease (moderate or severe)	3
Solid tumor (with metastases)	6
<b>Total score</b>	

Etienne, A, Esterni, B, Charbonnier, A, et al. Comorbidity is an independent predictor of complete remission in elderly patients receiving induction chemotherapy for acute myeloid leukemia. *Cancer* 2007; 109:1376. Copyright © 2007 American Cancer Society. This material is reproduced with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

Table 2. Charlson comorbidity index (CCI)

HCT comorbidity index – The hematopoietic cell transplantation specific comorbidity index (HCT-CI) was designed to predict outcomes in patients undergoing hematopoietic cell transplantation (HCT) (table 3). It has had mixed results in predicting outcome in older adults with AML.

Comparison of Charlson and HCTCI scoring systems

Comorbidity	CCI score	CCI definition	HCTCI score	HCTCI-definition
Mild pulmonary	1	Dyspnea on moderate activity (or with attacks, eg asthma)	0	Dyspnea on moderate activity or DLco or FEV <sub>1</sub> 90-80 percent
Moderate pulmonary	1	Dyspnea on slight activity	2	Dyspnea on slight activity or DLco or FEV <sub>1</sub> >65 <80 percent
Severe pulmonary	1	Dyspnea at rest or requires oxygen	3	Dyspnea at rest or requires oxygen or DLco or FEV <sub>1</sub> ≤65 percent
Cardiac	1	HF (symptomatic and requiring tx) MI	1	CAD (one or more vessel-coronary artery stenosis requiring medical treatment, stent, or bypass graft), HF, MI, or EF <50 percent
Mild hepatic	1	Chronic hepatitis or cirrhosis	1	Chronic hepatitis or bilirubin >ULN-1.5 × ULN, or AST/ALT >ULN-2.5 × ULN
Moderate/severe hepatic	3	Cirrhosis with portal hypertension ± bleeding varices	3	Cirrhosis or fibrosis or bilirubin >1.5 × ULN, or AST/ALT >2.5 × ULN
Moderate/severe renal	2	Serum creatinine >265.2 μmol/l, renal dialysis, or renal transplant	2	Serum creatinine >176.8 μmol/l, renal dialysis, or renal transplant
Prior solid tumour	2	Initially treated in the last 5 years	3	Treated at any time point in the patient's past history, excluding non-melanoma skin cancer
Metastatic cancer	6	Metastatic cancer		
Psychiatric disturbance*	N/A	N/A	1	Depression/anxiety requiring psychiatric consult or treatment
Infection*	N/A	N/A	1	Requiring continuation of anti-microbial treatment after day 0
Obesity*	N/A	N/A	1	Patients with a body mass index >35 kg/m <sup>2</sup>

CCI: Charlson comorbidity index; HCTCI: hematopoietic cell transplantation comorbidity index; FEV<sub>1</sub>: forced expiratory volume in one second; DLco: lung diffusion capacity of carbon monoxide; HF: heart failure; MI: myocardial infarction; CAD: coronary artery disease; EF: ejection fraction; ULN: upper limit of normal; AST/ALT: aspartate transaminase/alanine transaminase.

\* Added and validated HCTCI scored conditions.

Reproduced with permission from: Giles, PJ, Borhakar, G, Ravandi, F, et al. The hematopoietic cell transplantation comorbidity index score is predictive of early death and survival in patients over 60 years of age receiving induction therapy for acute myeloid leukemia. *Br J Haematol* 2007; 136:624. Copyright © 2007 Blackwell Publishing Ltd.

Table 3. Hematopoietic cell transplantation specific comorbidity index

A retrospective study of 177 patients over 60 years of age receiving induction chemotherapy for AML reported HCT-CI scores of zero, 1 to 2, and greater than 2 in 22, 30, and 48 percent

of patients, respectively [14]. Corresponding early death rates were 3, 11, and 29 percent, respectively. The same groups had median overall survival times of 45, 31, and 19 weeks, respectively. A second retrospective study evaluated the use of the HCT-CI in 92 patients age 80 or above with newly diagnosed AML offered induction chemotherapy [13]. Intensive therapy was given to 64 percent while the remainder elected supportive care. HCT-CI scores of zero to 1, 2 to 3, and 4 or greater were seen in 20, 35, and 45 percent, respectively. Patients with a HCT-CI score greater than 4 had a similar median survival when compared to those with a HCT-CI score of zero or 1 whether they received supportive care (1.9 versus 1.4 months) or intensive chemotherapy (3.5 versus 4.2 months).

Family discussions – A discussion with the patient and family members should include a review of the following

Prognostic information allowing them to make informed decisions on the type of treatment to be pursued [12]. Regardless of treatment choice, patients and their family members often report not being offered alternative treatment options and tend to overestimate the chance of cure [15]. Written consent forms required for clinical trials may serve an educational role, even for those who do not desire to enter into a formal study. Who has durable power of attorney for health issues if the patient becomes unable to make decisions? Does the patient have an updated will? Do other members of the family know where this information is kept? Will the family have access to adequate funds while the patient is hospitalized? A discussion concerning "code" status and the possibility that the patient might need to be transferred to an intensive care unit, with its attendant morbidity and mortality [16]. This should include issues related to "do not resuscitate" and "do not intubate" orders, such that the patient and family can make properly informed decisions on these matters. (See "Ethics in the intensive care unit: Informed consent; withholding and withdrawal of life support; and requests for futile therapies".) The effect on the patient's employment. Most patients will not be able to return to even part-time work until the completion of induction and consolidation chemotherapy.

### 3. Outcomes in older compared to younger patients

Overview – Overall survival rates for AML decrease as age increases (figure 1). Most series of older patients with newly diagnosed AML have noted CR rates between 40 and 60 percent [2,4,5,8,12,17-21]. While suitably selected older patients given aggressive induction therapy may achieve CR at a rate approximating that of younger patients [12], others may spend a significant proportion of their remaining life in a hospital setting receiving treatment.

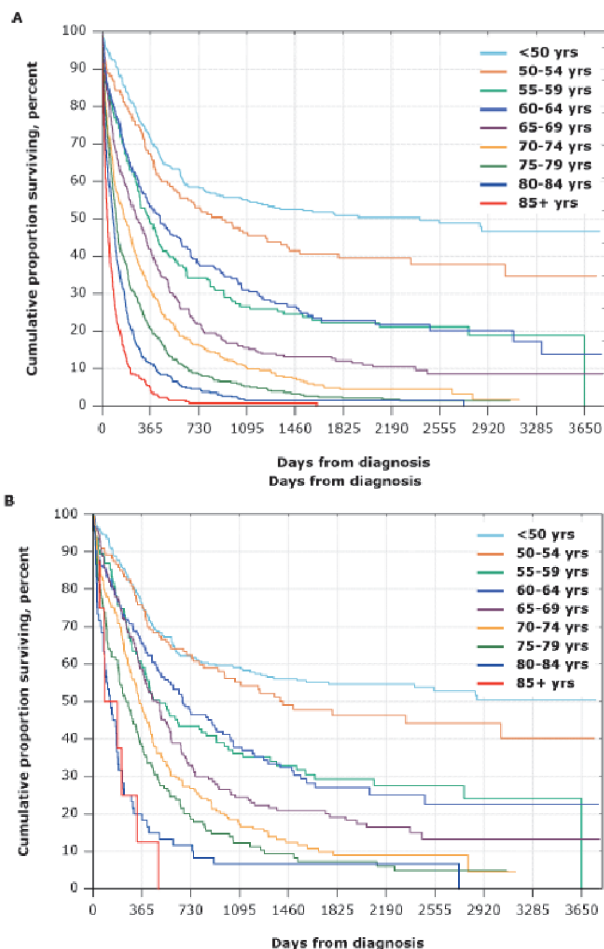
Older age, defined in most studies as over age 55, 60, or 65, is an independent poor prognostic factor in AML. Such patients have, in comparison with younger patients.

Poorer performance status Higher incidence of multidrug resistance Lower percentage of favorable cytogenetics Higher percentage of unfavorable cytogenetics Higher treatment-related morbidity and mortality Higher incidence of treatment-resistant disease Lower complete remission rates, shorter remission durations, and shorter median overall survival Fewer opportunities for allogeneic hematopoietic cell transplantation.

An analysis of Medicare claims for 2657 older patients with AML diagnosed between 1991 and 1996 underscored the grim prognosis for AML in the older patient.

Median survival for all patients was two months, with a two-year overall survival of 6 percent. For patients  $\geq 85$  years of age, median survival was only one month. Only 30 percent of patients received chemotherapy; when compared with those not receiving chemotherapy,

they tended to be younger (average age 73 versus 78 years) and live longer (median survival seven versus one month). Of those older patients dying from AML during the follow-up period of the study (94 percent of the sample), 31 percent of their remaining days had been spent in an inpatient facility.



Overall survival according to age irrespective of management (Panel A,  $n = 2767$ ), and patients with de novo AML, fit for intensive treatment, and with WHO/ECOG performance status 0 to II (Panel B,  $n = 1229$ )

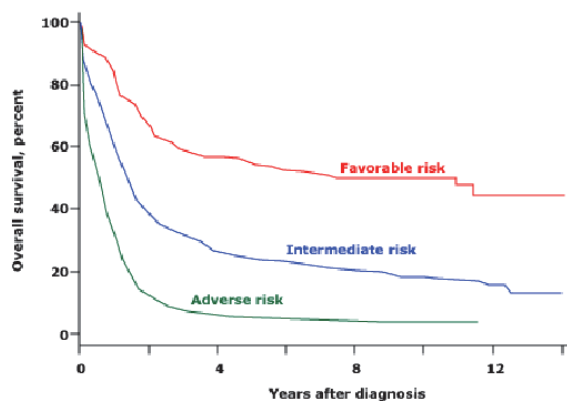
Fig. 1. Overall survival rates for AML decrease as age increases.

The outcomes might be better if more patients were offered induction chemotherapy. A retrospective analysis of 2767 patients with non-APL AML from the Swedish acute leukemia registry reported that early death rates (ie, death within 30 days of diagnosis) were considerably lower in patients receiving intensive induction chemotherapy when compared with those who received palliative therapy, even when stratified for performance status, however it remains possible that patients with a better prognosis were more likely to be

offered induction chemotherapy [4]. The difference between 30-day mortality rates for the two groups ranged from 16 to 35 percent. Patients who had de novo AML, were "fit" for intensive chemotherapy, had an ECOG performance status of zero to 2, and were age 16 to 55, 56 to 65, 66 to 75, and 76 to 89 had median overall survival times of 7 years, 18 months, 14 months, and 6 months, respectively.

Prognostic factors – A number of risk factors have been identified which occur more frequently in the older patient and appear to contribute to the worse outcome. The major independent prognostic factors in older adults with AML are Age Cytogenetics Performance status Secondary leukemia White blood cell count at diagnosis Multidrug resistance-1 (P-glycoprotein) expression.

The cytogenetic abnormalities most often associated with treatment failure in young patients with AML (eg, abnormalities of chromosomes 5 or 7 or complex karyotypes) are considerably more common in older patients, occurring in 32 to 57 percent of patients in two series [25,27-30]. Conversely, all of the "favorable" cytogenetic abnormalities, such as t(8;21), t(15;17), or inv(16), are more common in younger subjects and are responsible in part for their better disease-free survival, Figure 2.



This figure illustrates overall survival in adult subjects with acute myeloid leukemia (AML), according to the following cytogenetic risk categories: Favorable risk (median survival 7.6 years): t(8;21); inv(16) or t(16;16); del(9q). Intermediate risk (median survival 1.3 years): normal karyotype; -Y; del(5q); loss of 7q; t(9;11); +11; del(11q); abn(12p); +13; del(20q); +21. Adverse risk (median survival 0.5 years): complex karyotype ( $\geq 3$  abnormalities); inv(3) or t(3;3); t(6;9); t(6;11); -7; +8 (sole abnormality); +8 with one other abnormality other than t(8;21), t(9;11), inv(16), or t(16;16); t(11;19)(q23;p13.1).

Fig. 2. Overall survival in aml according to the cytogenetic study.

#### 4. Overview of treatment

Goals – The goal of remission induction chemotherapy is the rapid restoration of normal bone marrow function and attainment of complete remission.

Induction therapy aims to reduce the total body leukemia cell population from approximately  $10^{12}$  to below the cytologically detectable level of about  $10^9$  cells. It is generally assumed, however, that a substantial burden of leukemia cells persists undetected (ie, minimal residual disease), leading to relapse within a few weeks or months if no further therapy were administered.

Postinduction or "remission consolidation" therapy usually comprises one or more courses of chemotherapy or hematopoietic cell transplantation (HCT). It is designed to eradicate residual leukemia, allowing the possibility of cure. Rates of relapse and death are quite low after three to four years in remission, and most such patients are long-term disease-free survivors.

Decision to treat – After the diagnosis of AML has been established, the physician and staff must present the goals of therapy, as well as the side effects of treatment, to the patient and family. For almost all patients, this discussion can emphasize the potential benefits of intensive treatment with regard to both the short and long term outcome. Remission induction, even if short-lived, is an appropriate goal for most patients with AML.

Patients who achieve a remission have an improved quality of life compared with those patients who receive palliative therapy likely because they require fewer hospitalizations, transfusions, and antibiotics [4]. Attainment of CR following intensive chemotherapy is required in order to assure meaningful prolongation of life.

Occasionally, intensive treatment with the intent to achieve CR may be less advisable because of advanced patient age, debility, presence of significant co-existing medical problems, and/or prior chemotherapy. Patients unlikely to survive treatment can be identified by their poor performance status using the Karnofsky or ECOG (Zubrod) performance.

In addition, there are a few patients with "acute leukemia" by the usual quantitative criteria of >20 percent bone marrow blast cells whose disease has a much more smoldering course. These patients suffer from bone marrow failure and pancytopenia more than hyperleukocytosis. Their survival may be equally long and their quality of life better, using transfusion support and antibiotics rather than intensive chemotherapy. This may be particularly true for the "hypoplastic/hypocellular" variant of AML. Supportive care may also be beneficial in acutely infected patients with advanced myelodysplastic syndromes. Occasionally, the clinical picture mimics AML, but resolves following treatment of the infection.

For otherwise healthy (ECOG performance status of two or less and few comorbidities) older adults with newly diagnosed AML, we suggest remission induction treatment, ideally on a clinical trial. For older patients with indolent AML, severe comorbidity, or high risk disease, we suggest the use of supportive care rather than standard induction chemotherapy.

It is frequently appropriate and necessary to repeat this discussion and counseling later during the patient's course, as a diagnosis of acute leukemia often leaves the patient and family unable to cope with the longer term consequences of this diagnosis until the patient has successfully passed through the initial weeks of chemotherapy and recovery.

INDUCTION – The best treatment strategy for older patients with AML remains controversial. Among the treatment options that have been evaluated are various forms of intensive or less-intensive chemotherapy, the administration of colony-stimulating factors to enhance neutrophil recovery, supportive therapy, low-dose cytarabine, high- or intermediate-dose cytarabine-based consolidation therapy, prolonged consolidation therapy, and maintenance treatment with interferon. Most of these studies have been disappointing.

Intensive chemotherapy – The best induction chemotherapy for older patients with AML remains to be identified. Intensive chemotherapy may be appropriate for selected patients with low or intermediate risk disease in whom the complete remission (CR) rate can be as



high as 70 to 80 percent . With this approach, median survival is approximately eight months, but 9 to 12 percent of patients will be alive at five years. Although pilot studies have used more intensive initial chemotherapy, a reasonable standard regimen for many older patients who are medically fit is seven days of continuous infusion cytarabine (ara-C, 100 mg/m<sup>2</sup> per day) plus three days of daunorubicin (60 or 90 mg/m<sup>2</sup> per day).

Randomized trials have investigated various modifications of cytarabine plus an anthracycline for the treatment of older adults with AML. In general, the choice of anthracycline (eg, daunorubicin, mitoxantrone, or idarubicin) does not appear to affect overall outcome. However, higher doses of anthracyclines may result in superior rates of complete remission (CR) without an apparent increase in toxicity.

For most older adults with favorable or intermediate risk AML and an ECOG performance status of two or less and few comorbidities, we suggest remission induction treatment with a combination of an anthracycline such as daunorubicin for three days and "standard" dose cytarabine for seven days rather than other chemotherapy regimens or supportive care alone. When induction treatment is chosen, it should be applied at sufficient dose intensity to provide the best chance of success. Further details on the administration of this regimen are presented separately as are recommendations for evaluation after completion of induction therapy.

Use of growth factors – Several groups have evaluated the effects of colony-stimulating factors (eg, GM-CSF, G-CSF, and glycosylated G-CSF) as an adjunct to intensive chemotherapy with largely disappointing results. The rationale for this approach is that older patients are particularly susceptible to infection and experience a higher infectious mortality rate during episodes of neutropenia. Shortening the duration of neutropenia might have a beneficial effect and improve the rate of complete remission.

What Treatment Options Are Available for Patients Who Are Not Candidates for Intensive Induction Therapy?

For those patients who are not considered to be candidates for intensive induction therapy, one would hope to identify agents and regimens that are more effective and less toxic to address the concerns regarding early induction death, inadequate response rate, and high risk of relapse. The NCRI AML 14 study was designed to allow for randomization of patients between intensive and nonintensive therapy, but only eight patients agreed to randomization[117,147]. As such, data available on novel agents comes from a variety of pilot and phase II studies with differing eligibility criteria. When evaluating the outcomes, it is important to also look at the characteristics of patients who were ultimately enrolled.

reviews available data from some of these studies .

As part of the NCRI AML 14 study, 212 patients who were deemed unfit for intensive treatment options by the local investigator were randomized to receive supportive care alone with hydroxyurea or cytarabine 20 mg twice daily by subcutaneous injection for 10 days every 4 to 6 weeks [95]. Outcome was improved for the low-dose (LD) cytarabine arm when compared with supportive care with hydroxyurea alone. CR was 18% versus 1%, and median survival was 575 days for those who achieved CR, compared with 66 days in nonresponders. DFS for responders was 8 months. Survival benefit was seen in all age groups, even those over age 75. As none of the patients with adverse cytogenetics achieved a CR, no survival benefit was, however, seen in that group. The early death rate was 39% at 8 weeks. Although no criteria were used to define unfit patients, 78% were over age 70, 27% had secondary AML, 30% had PS \_ 2, 27% had heart disease, 49% had other

comorbidities, and 59% had a poor risk score by the Wheatley Risk Index [90]. Based on this study, LD cytarabine became the standard of care for the treatment of patients felt to be unfit for intensive chemotherapy, although one could argue that it should not be given to those with poor risk cytogenetics.

The DNA methyltransferase inhibitors have been the subject of several recent studies. In a multicenter phase II study of 55 patients over age 60 with untreated AML, decitabine was administered for 5 days monthly until disease progression. [96]. With a median of three cycles, the overall response rate was 24%, median survival was 7.7 months, and 30-day mortality was 7%. Responses were seen in all cytogenetic risk groups, as well as in those patients with prior MDS. An alternate schedule of decitabine was reported by Blum et al [97,98]. Patients received an initial one to two courses of 10 days of decitabine, followed by a course over 3 to 5 days every 4 weeks for 1 year. Of the 53 patients with a median age of 74, 36% had secondary AML, and 34% had a complex karyotype.

Eighteen patients had a HCTCI score of  $\leq 3$ . There was a 64% response rate after a median of three cycles of therapy. CR occurred in all subsets, regardless of age, karyotype, presenting WBC, and prior AHD. One-year survival of poor risk patients was 30% (compared with 10% in patients with a similar Wheatley risk score in the AML 11 trial) [90].

In a study of azacitidine in AML with 20% to 30% blasts, patients who were deemed unfit for standard induction chemotherapy were randomized against either supportive care or LD cytarabine [99]. OS survival was superior in the azacitidine arm. There was a statistically significant difference seen in OS for patients with poor risk cytogenetics in favor of azacitidine, compared with conventional care regimens (12.3 vs 5.3 months, respectively, with 2-year OS of 38% vs 0%).

Gemtuzumab ozogamicin (GO) has been the subject of a recent study by the EORTC and GIMEMA leukemia groups (AML 19) [100].

In this randomized multicenter study, 84 patients were randomized to receive one of two schedules of GO at attenuated doses or best supportive care. The proportion of patients either achieving a response or maintaining stable disease was greater in patients who receive GO at a dose of 6 mg/m<sup>2</sup> on day 1 and 3 mg/m<sup>2</sup> on day 8, when compared with a schedule of GO 3 mg/m<sup>2</sup> on days 1, 3, and 5 (63% vs 38%, respectively). Results of the comparison with patients who were randomized to standard care are not yet available, and a phase III trial is ongoing.

Clofarabine has been studied as an agent in elderly patients with AML. In a phase II study of the agent in 112 patients over age 60 with untreated AML with at least one unfavorable baseline prognostic factor, there was a 46% response rate [101]. The median age of the patients was 71. Twenty-two percent of patients had a baseline PS of 2, 47% had a prior hematologic disorder (AHD) or secondary AML, 55% had an unfavorable karyotype, and 62% were  $\geq 70$ .

Overall response rate (ORR) was 39% for patients  $\geq 70$ , 32% for PS 2, 51% for patients with AHD, 54% for intermediate karyotype and 42% for unfavorable karyotype, and 38% for patients with three risk factors. Median DFS was 37 weeks, and median OS was 41 weeks for all patients, 59 weeks for patients with CR/complete remission with incomplete platelet recovery (CRp), and 72 weeks for patients with CR. Early death rate (within 60 days) was 16%.

In two consecutive European studies of 106 untreated older patients with AML who were considered unfit for chemotherapy, participants were given four to six 5-day courses of

clofarabine[70,102]. In the UWCM (University of Wales College of Medicine)-001 study, patients who were either over age 70 (68%) or over age 60, with a PS of 2 or cardiac comorbidity, were treated with clofarabine for 5 days every 28 days for 2 to 4 courses. In the BIOV-121 study, patients were treated for 5 days every 4 to 6 weeks for up to six courses. All patients were age  $\geq$  65 and deemed unfit for chemotherapy.

Overall, 36% of patients had a PS  $\geq$  2, 30% had adverse risk cytogenetics, 46% had Wheatley poor risk disease, and 65% were age  $\geq$  70. The ORR was 48%, and the median OS was 19 weeks for all and 45 weeks for those who attained a CR/completeremission with incomplete blood count recovery (CRI). Responses were seen in patients with adverse cytogenetics (44% ORR), patients with secondary AML (31%), and patients age  $\geq$  70 (49%).

The death rate within 30 days was 18%. A novel agent, laromustine (VNP40101M), a sulfonylhydrazine alkylating agent, has been studied in 85 patients with poor risk AML age  $\geq$  60 years. 51 Patients received one to two cycles of laromustine at a dose of 600 mg/m<sup>2</sup>, followed by one cycle of cytarabine. Seventy-eight percent of patients were age  $\geq$  70, 47% had an adverse karyotype, 41% had a PS of 2, 77% had pulmonary disease, 73% had cardiac disease, and 3% had hepatic disease. All patients with unfavorable karyotype or ECOG PS had at least one other risk factor at the time of enrollment. Seventy-five percent of patients had  $\geq$  3 risk factors. The ORR was 32% and was similar in patients over age 70 (32%), with a PS of 2 (32%), with baseline pulmonary or cardiac dysfunction (27%-34%).

There was a 14% 30-day mortality. OS was 3.2 months (12.4 months for those with CR/CRp), and 1-year survival was 21% (52% for those with CR/CRp).

These phase II studies are encouraging, in that responses are seen in all poor risk categories, and early death rates are acceptable. Randomized trials are needed. Although randomized trials of intensive versus nonintensive therapy have not been successful, the ongoing AML 16 trial was designed to randomize patients who are considered not fit for intensive treatment to LD cytarabine versus LD cytarabine with GO, LD cytarabine with arsenic trioxide or tipifarnib, or LD clofarabine.<sup>52</sup> The arsenic arm has been closed because of ineffectiveness with CR/CRI of 29%, compared with 24% and a 12-month OS of 27%, compared with 41%. The other arms continue to accrue patients.

**POST REMISSION THERAPY** – While a substantial percentage of older adults will attain a complete remission (CR) with induction chemotherapy, virtually all of these patients will relapse within a median of four to eight months unless given additional cytotoxic therapy. Even with post-remission therapy, relapses are common. Only about 10 percent of older adults, and generally only those with favorable or intermediate risk disease, attain long-term survival after the administration of post-remission therapy.

Post-remission therapy aims to destroy leukemia cells that survived induction chemotherapy but are undetectable by conventional studies. There are two generally accepted options for post-remission therapy: consolidation chemotherapy and allogeneic hematopoietic cell transplantation (HCT). Consolidation chemotherapy is less intensive and has a lower early mortality rate, but allogeneic HCT provides a graft-versus-tumor effect that decreases relapse rates. In younger patients, consolidation chemotherapy is usually given to patients with favorable risk disease while HCT is used for patients with unfavorable risk disease. The optimal treatment for intermediate risk disease is unknown. Evidence regarding the therapeutic benefit of any consolidation therapy in older patients with AML is limited and its value has remained uncertain. Newly discovered genetic

markers are helping to refine the risk stratification. A detailed description of these options in younger adults is presented separately. Post-remission therapy in older adults is complicated by high rates of treatment related toxicity. Older adults are generally not candidates for a fully myeloablative allogeneic HCT, but a subset may be able to undergo nonmyeloablative HCT after reduced intensity conditioning regimens. A choice among these strategies is generally made based upon the risk stratification of the patient's tumor and the patient's performance status and comorbidities that might affect tolerance of intensive therapy. A phase III trial demonstrated that post-remission therapy with single agent gemtuzumab ozogamicin did not improve clinical outcomes (probability of relapse, overall survival, or disease free survival), but added toxicities[75].

**Consolidation chemotherapy – High dose cytarabine (HiDAC)** is the standard consolidation chemotherapy for younger adults with AML of a favorable risk, but is associated with unacceptably high rates of severe toxicity and early death in older adults that counteract any improvement in efficacy over standard dose cytarabine. Instead, consolidation therapy with two cycles of daunorubicin (30 to 45 mg/m<sup>2</sup> for two days) and cytarabine (ara-C, 100 mg/m<sup>2</sup> per day for five days) for older adults is preferred. The use of consolidation chemotherapy in younger adults is presented separately.

**Nonmyeloablative transplantation – Allogeneic hematopoietic cell transplantation (allo-HCT)** is the preferred treatment for younger adults with unfavorable risk AML because of its graft-versus-leukemia effect. However, allo-HCT is associated with a very high treatment-related mortality rate in older patients that precludes its general use. Instead, various reduced intensity or nonmyeloablative [85] allo-HCT regimens have been employed in fit older adults. However, the comparable efficacy of this approach remains to be proven and a randomized, multinational trial by the European Group for Blood and Marrow Transplantation evaluating alloSCT versus conventional consolidation therapy in elderly patients is currently accruing patients. The use of allo-HCT in younger adults is presented separately, as is additional information on nonmyeloablative allo-HCT.

The development of less toxic and better tolerated nonmyeloablative regimens capable of inducing a state of mixed chimerism may allow allo-HCT to be performed in patients with AML and advanced age or co-morbidity, with the hope that such regimens would result in lower rates of treatment-related mortality without sacrificing relapse-free and overall survival, and with a reasonable balance between GVHD and the graft-versus-tumor effect. Additional experience with this approach is awaited.

**SUPPORTIVE CARE –** For older patients with indolent AML, severe comorbidity, or high risk disease, we suggest the use of supportive care rather than induction chemotherapy. Supportive care can include the use of red blood cell and platelet transfusions, antibiotics, and control of leukocytosis with agents such as low-dose cytarabine or hydroxyurea.

**Low-dose cytarabine –** While not curative, many committees, including the British Committee for Standards in Hematology, consider low-dose cytarabine to be the standard against which other palliative treatments for AML in the older patient should be evaluated.

A number of trials have investigated the use of low-dose cytarabine in older subjects with AML, both for induction and later for maintenance of remission. As an example, investigators in France randomly assigned 87 patients >65 to receive either intensive chemotherapy with cytarabine and rubidazole (a daunorubicin analogue) or low-dose subcutaneous cytarabine (10 mg/m<sup>2</sup> every 12 hours for 21 days). Although the number of complete remissions was greater with intensive chemotherapy, the early death rate was also higher.

Other supportive measures – Other measures of supportive care include the use of leukocyte-depleted, irradiated red blood cell and platelet transfusions as needed and the use of antibiotics to treat infections. As described above, patients treated with supportive care alone spend a similar amount of time in the hospital compared with those who receive intensive chemotherapy.

### 5. Approach to the elderly patient with AML

AML is a disease of the elderly, with the majority of patients over age 60. As our population ages, that percentage will only increase.

Unfortunately, the standard regimens that are successful in treating younger patients with AML are not as beneficial in the majority of older patients with the disease. Figure 3 outlines my approach to the elderly patient with AML. Understanding of the disease biology, as well as the prognostic factors associated with the host, allows us to better determine which patients are likely to benefit from standard therapy and which require alternative approaches. Objective scoring systems are being developed that allow us to define patients unfit for intensive chemotherapy on the basis of increased risk of induction death, low response rate, and/or low long-term DFS. Optimal induction and postremission therapy for patients appropriate for intensive therapy have yet to be defined, again, because results are not satisfactory with our current regimens, even in those patients who do not have definable poor prognostic factors. When compared with young patients with similar disease-related features, outcomes are inferior. For patients who are not candidates for intensive therapy because of comorbid conditions, low-intensity therapies appear to be superior to palliative care alone. Whenever possible, patients should be enrolled in clinical trials that will allow us to address these issues.

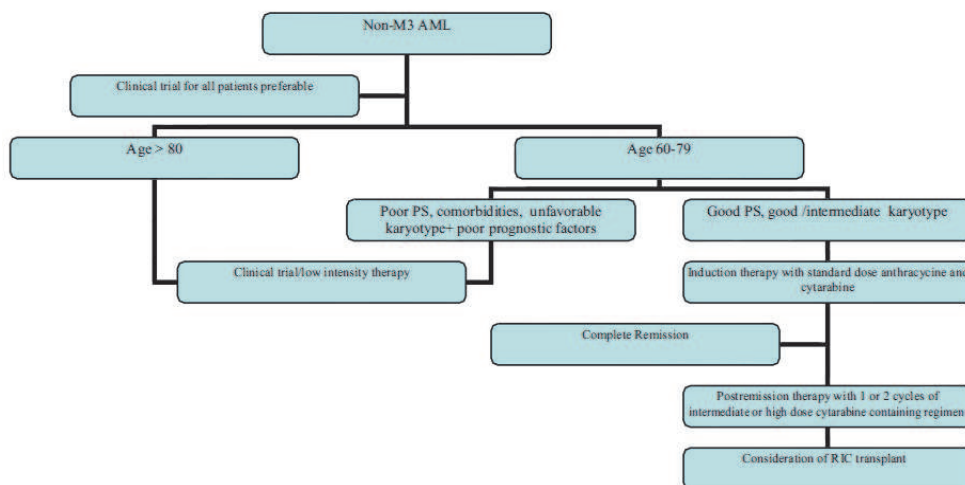


Fig. 3. Outlines my approach to the elderly patient with AML.

## 6. References

- [1] Surveillance Epidemiology and End Results (SEER) Program. Limited use-data (1973 – 2004). National Cancer Institute D, Surveillance Research Program, Cancer Statistics Branch. SEER Web site. [http:// www.seer.cancer.gov](http://www.seer.cancer.gov). Accessed April 2007.
- [2] Juliusson G, Antunovic P, Derolf A, et al. Age and acute myeloid leukemia: real world data on decision to treat and outcomes from the Swedish Acute Leukemia Registry. *Blood*. 2009;113:4179 – 4187.
- [3] Pulte D, Gondos A, Brenner H, Pulte D, Gondos A, Brenner H. Improvements in survival of adults diagnosed with acute myeloblastic leukemia in the early 21st century. *Haematologica*. 2008;93:594 – 600.
- [4] Buchner T, Berdel WE, Haferlach C, et al. Age-related risk profile and chemotherapy dose response in acute myeloid leukemia: a study by the German Acute Myeloid Leukemia Cooperative Group. *J Clin Oncol*. 2009;27:61– 69.
- [5] Lerch E, Espeli V, Zucca E, et al. Prognosis of acute myeloid leukemia in the general population: data from southern Switzerland. *Tumori*. 2009;95:303–310.
- [6] Alibhai SM, Leach M, Minden MD, et al. Outcomes and quality of care in acute myeloid leukemia over 40 years. *Cancer*. 2009;115:2903–2911.
- [7] Appelbaum F, Gundacker H, Head DR, et al. Age and acute myeloid leukemia. *Blood*. 2006;107:3481–3485.
- [8] Rao AV, Valk PJ, Metzeler KH, et al. Age-specific differences in oncogenic pathway dysregulation and anthracycline sensitivity in patients with acute myeloid leukemia. *J Clin Oncol*. 2009;27:5580 –5586.
- [9] Appelbaum FR, Baer MR, Carabasi MH, et al. NCCN practice guidelines for acute myelogenous leukemia. *Oncology*. 2000;14: 53–61.
- [10] Dohner H, Estey EH, Amadori S, et al. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. *Blood*. 2010;115:453– 474.
- [11] Morra E, Barosi G, Bosi A, et al. Clinical management of primary non-acute promyelocytic leukemia acute myeloid leukemia: Practice Guidelines by the Italian Society of Hematology, the Italian Society of Experimental Hematology, and the Italian Group for Bone Marrow Transplantation. *Haematologica*. 2009;94:102–112.
- [12] Lowenberg B, Ossenkoppele GJ, van Putten W, et al. Highdose daunorubicin in older patients with acute myeloid leukemia. *N Engl J Med*. 2009;361:1235–1248.
- [13] Pautas C, Merabet F, Thomas X, et al. Randomized study of intensified anthracycline doses for induction and recombinant interleukin-2 for maintenance in patients with acute myeloid leukemia age 50 to 70 years: results of the ALFA-9801 study. *J Clin Oncol*. 2010;28:808–814.
- [14] Burnett AK, Milligan D, Goldstone A, et al. The impact of dose escalation and resistance modulation in older patients with acute myeloid leukaemia and high risk myelodysplastic syndrome: the results of the LRF AML 14 trial. *Br J Haematol*. 2009;145:318 –332.
- [15] Cripe LD, Uno H, Paietta EM, et al. Zosuquidar, a novel modulator of P-glycoprotein, does not improve the outcome of older patients with newly diagnosed acute myeloid leukemia: a randomized, placebo-controlled, trial of the Eastern

- Cooperative Oncology Group (ECOG 3999). *Blood*. 2010 Aug 17. [Epub ahead of print]
- [16] Lancet J, Gotlib J, Wetzler M, et al. Phase I/II study of the P-glycoprotein (Pgp) inhibitor zosuquidar administered by continuous infusion (CIV) with daunorubicin (DNR) and cytarabine (ARA-C) as primary therapy in older patients with Pgp-positive acute myeloid leukemia (AML) [abstract]. *Blood*. 2007;110.
- [17] Chauncey TR, Gundacker H, Shadman M, et al. Sequential phase II Southwest Oncology Group studies (S0112 and S0301) of daunorubicin and cytarabine by continuous infusion, without and with ciclosporin, in older patients with previously untreated acute myeloid leukaemia. *Br J Haematol*. 2009;148:48 -58.
- [18] Burnett A, Russell N, Kell J, et al. European development of clofarabine as treatment for older patients with acute myeloid leukemia considered unsuitable for intensive chemotherapy [abstract]. *J Clin Oncol*. 2010;28.
- [19] Faderl S, Erba HP, Claxton DF, et al. Clofarabine produces durable remissions in older patients with AML with unfavorable prognostic factors and multiple comorbidities [abstract 4155]. *Blood*. 2009;114.
- [20] Faderl S, Ravandi F, Huang X, et al. A randomized study of clofarabine versus clofarabine plus low-dose cytarabine as front-line therapy for patients aged 60 years and older with acute myeloid leukemia and high-risk myelodysplastic syndrome. *Blood*. 2008;112:1638 -1645.
- [21] Mayer RJ, Davis RB, Schiffer CA, et al. Intensive postremission chemotherapy in adults with acute myeloid leukemia. *N Engl J Med*. 1994;331:896 -903.
- [22] Rowe JM, Neuberg D, FriedenberG W, et al. A phase 3 study of three induction regimens and of priming with GM-CSF in older adults with acute myeloid leukemia. A trial by the Eastern Cooperative Oncology Group. *Blood*. 2004;103:479-485.
- [23] Lowenberg B, Beck J, Graux C, et al. Gemtuzumab ozogamicin as postremission treatment in AML at 60 years of age or more: results of a multicenter phase 3 study. *Blood*. 2010;115:2586-2591.
- [24] Baer MR, George SL, Caligiuri MA, et al. Low-dose interleukin-2 immunotherapy does not improve outcome of patients age 60 years and older with acute myeloid leukemia in first complete remission: Cancer and Leukemia Group B Study 9720. *J Clin Oncol*. 2008;26:4934 - 4939.
- [25] Jehn U, Suciú S, Thomas X, et al. Non-infusional vs intravenous consolidation chemotherapy in elderly patients with acute myeloid leukemia: final results of the EORTC-GIMEMA AML-13 randomized phase III trial. *Leukemia*. 2006;20:1723 - 1730.
- [26] Thomas X, Suciú S, Rio B, et al. Autologous stem cell transplantation after complete remission and first consolidation in acute myeloid leukemia patients aged 61 - 70 years: results of the prospective EORTC-GIMEMA AML-13 study. *Haematologica*. 2007;92:389 - 396.
- [27] Goldstone A, Burnett A, Wheatley K, Smith AG, Hutchinson M, Clark R. Attempts to improve treatment outcomes in acute myeloid leukemia (AML) in older patients: the results of the United Kingdom Medical Research Council AML11 trial. *Blood*. 2001;98:1302 - 1311.

- [28] Gardin C, Turlure P, Fagot T, et al. Postremission treatment of elderly patients with acute myeloid leukemia in first complete remission after intensive induction chemotherapy: results of the multicenter randomized Acute Leukemia French Association (ALFA) 9803 trial. *Blood*. 2007;109:5129 – 5135.
- [29] Schlenk RF, Frohling S, Hartmann F, et al. Intensive consolidation versus oral maintenance therapy in patients 61 years or older with acute myeloid leukemia in first remission: results of second randomization of the AML HD98-B treatment trial. *Leukemia*. 2006;20:748 – 750.
- [30] Prebet T, Boissel N, Reutenauer S, et al. Acute myeloid leukemia with translocation (8;21) or inversion (16) in elderly patients treated with conventional chemotherapy: a collaborative study of the French CBF-AML intergroup. *J Clin Oncol*. 2009;27:4747 – 4753.
- [31] Sekeres MA, Elson P, Kalaycio ME, et al. Time from diagnosis to treatment initiation predicts survival in younger, but not older, acute myeloid leukemia patients. *Blood*. 2009;113:28 – 36.
- [32] Chevallier P, Blaise D, Milpied N, et al. Reduced intensity conditioning (RIC) allogeneic stem cell transplantation for patients aged  $\geq 60$  years: a retrospective study of 629 patients from the Societe Francaise De Greffe De Moelle et de therapie cellulaire (SFGM-TC). *Blood*. 2009;114:84 – 85.
- [33] Roellig C, Thiede C, Gramatzki M, et al. A novel prognostic model in elderly patients with acute myeloid leukemia: results of 909 patients entered into the prospective AML96 trial. *Blood*. 2010;116:971 – 978.
- [34] Estey E, de Lima M, Tibes R, et al. Prospective feasibility analysis of reduced-intensity conditioning (RIC) regimens for hematopoietic stem cell transplantation (HSCT) in elderly patients with acute myeloid leukemia (AML) and high-risk myelodysplastic syndrome (MDS). *Blood*. 2007;109:1395 – 1400.
- [35] Kurosawa S, Yamaguchi T, Uchida N, et al. Comparison of allogeneic hematopoietic cell transplantation and chemotherapy as post-remission strategy in elderly patients with non-M3 AML in CR1: retrospective analysis with 1036 patients [abstract 524]. *Blood*. 2009;114.
- [36] Juliusson G, Billstrom R, Gruber A, et al. Attitude towards remission induction for elderly patients with acute myeloid leukemia influences survival. *Leukemia*. 2006;20:42 – 47.
- [37] Grimwade D, Walker H, Harrison G, et al. The predictive value of hierarchical cytogenetic classification in older adults with acute myeloid leukemia (AML): analysis of 1065 patients entered into the United Kingdom Medical Research Council AML11 trial. *Blood*. 2001;98:1312 – 1320.
- [38] Wheatley K, Brookes CL, Howman AJ, et al. Prognostic factor analysis of the survival of elderly patients with AML in the MRC AML11 and LRF AML14 trials. *Br J Haematol*. 2009;145:598 – 605.
- [39] Kantarjian H, O'Brien S, Cortes J, et al. Results of intensive chemotherapy in 998 patients age 65 years or older with acute myeloid leukemia or high-risk myelodysplastic syndrome: predictive prognostic models for outcome. *Cancer*. 2006;106:1090 – 1098.
- [40] Giles FJ, Borthakur G, Ravandi F, et al. The haematopoietic cell transplantation comorbidity index score is predictive of early death and survival in patients over 60



- years of age receiving induction therapy for acute myeloid leukaemia. *Br J Haematol.* 2007;136:624 - 627.
- [41] Malfuson JV, Etienne A, Turlure P, et al. Risk factors and decision criteria for intensive chemotherapy in older patients with acute myeloid leukemia. *Haematologica.* 2008;93:1806 - 1813.
- [42] Rollig C, Aulitzky WE, Bodenstern H, et al. Risk stratification and prognostic factors in elderly AML patients— updated results of 909 patients entered into the prospective AML96 trial [abstract 329]. *Blood.* 2009;114.
- [43] Burnett AK, Milligan D, Prentice AG, et al. A comparison of low-dose cytarabine and hydroxyurea with or without all-trans retinoic acid for acute myeloid leukemia and high-risk myelodysplastic syndrome in patients not considered fit for intensive treatment. *Cancer.* 2007;109:1114 - 1124.
- [44] Cashen AF, Schiller GJ, O' Donnell MR, et al. Multicenter, phase II study of decitabine for the first-line treatment of older patients with acute myeloid leukemia. *J Clin Oncol.* 2010;28:556 - 561.
- [45] Blum W, Garzon R, Klisovic RB, et al. Clinical response and miR-29b predictive significance in older AML patients treated with a 10-day schedule of decitabine. *Proc Natl Acad Sci U S A.* 2010;107:7473 - 7478.
- [46] Blum W, Klisovic R, Liu S, et al. Preliminary results of a phase II study of low dose decitabine as a single agent in older patients (age  $\geq$ 60) with previously untreated acute myeloid leukemia (AML) [abstract 2957]. *Blood.* 2008;112.
- [47] Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Azacitidine prolongs overall survival compared with conventional care regimens in elderly patients with low bone marrow blast count acute myeloid leukemia. *J Clin Oncol.* 2010;28:562 - 569.
- [48] Amadori S, Succi S, Selleslag D, et al. Randomized trial of two schedules of low-dose gemtuzumab ozogamicin as induction monotherapy for newly diagnosed acute myeloid leukaemia in older patients not considered candidates for intensive chemotherapy. (A phase II study of the EORTC and GIMEMEA leukaemia groups (AML-19).) *Br J Haematol.* 2010;149:376 - 382.
- [49] Kantarjian HM, Erba HP, Claxton D, et al. Phase II study of clofarabine monotherapy in previously untreated older adults with acute myeloid leukemia and unfavorable prognostic factors. *J Clin Oncol.* 2010;28:549 - 555.
- [50] Burnett AK, Baccharani M, Johnson P, et al. A phase II study (biov-121) of clofarabine monotherapy first line in patients aged 65 years or older with acute myeloid leukemia for whom standard intensive chemotherapy is not considered suitable [abstract 425]. *Blood.* 2006;108.
- [51] Schiller GJ, O' Brien SM, Pigneux A, et al. Single-agent laromustine, a novel alkylating agent, has significant activity in older patients with previously untreated poor-risk acute myeloid leukemia. *J Clin Oncol.* 2010;28:815 - 821.
- [52] Russell NH, Hills RK, Hunter AE, et al. Low dose ara-C versus low dose ara-C and arsenic trioxide: the UK NCRI AML16 "pick a winner" comparison [abstract 486]. *Blood.* 2009;114.
- [53] Schiffer, CA. "I am older, not elderly," said the patient with acute myeloid leukemia. *J Clin Oncol* 2010; 28:521.
- [54] Appelbaum, FR, Gundacker, H, Head, DR, et al. Age and acute myeloid leukemia. *Blood* 2006; 107:3481.

- [55] Kantarjian, H, O'Brien, S, Cortes, J, et al. Results of intensive chemotherapy in 998 patients age 65 years or older with acute myeloid leukemia or high-risk myelodysplastic syndrome: predictive prognostic models for outcome. *Cancer* 2006; 106:1090.
- [56] Juliusson, G, Antunovic, P, Derolf, A, et al. Age and acute myeloid leukemia: real world data on decision to treat and outcomes from the Swedish Acute Leukemia Registry. *Blood* 2009; 113:4179.
- [57] Löwenberg, B, Ossenkoppele, GJ, van Putten, W, et al. High-dose daunorubicin in older patients with acute myeloid leukemia. *N Engl J Med* 2009; 361:1235.
- [58] Repetto, L, Fratino, L, Audisio, RA, et al. Comprehensive geriatric assessment adds information to Eastern Cooperative Oncology Group performance status in elderly cancer patients: an Italian Group for Geriatric Oncology Study. *J Clin Oncol* 2002; 20:494.
- [59] Wedding, U, Röhrig, B, Klippstein, A, et al. Impairment in functional status and survival in patients with acute myeloid leukaemia. *J Cancer Res Clin Oncol* 2006; 132:665.
- [60] Löwenberg, B, Suci, S, Archimbaud, E, et al. Mitoxantrone versus daunorubicin in induction-consolidation chemotherapy--the value of low-dose cytarabine for maintenance of remission, and an assessment of prognostic factors in acute myeloid leukemia in the elderly: final report. European Organization for the Research and Treatment of Cancer and the Dutch-Belgian Hemato-Oncology Cooperative Hovon Group. *J Clin Oncol* 1998; 16:872.
- [61] Wahlin, A, Markevärn, B, Golovleva, I, Nilsson, M. Prognostic significance of risk group stratification in elderly patients with acute myeloid leukaemia. *Br J Haematol* 2001; 115:25.
- [62] Wheatley, K, Brookes, CL, Howman, AJ, et al. Prognostic factor analysis of the survival of elderly patients with AML in the MRC AML11 and LRF AML14 trials. *Br J Haematol* 2009; 145:598.
- [63] Etienne, A, Esterni, B, Charbonnier, A, et al. Comorbidity is an independent predictor of complete remission in elderly patients receiving induction chemotherapy for acute myeloid leukemia. *Cancer* 2007; 109:1376.
- [64] Estey, E. Acute myeloid leukemia and myelodysplastic syndromes in older patients. *J Clin Oncol* 2007; 25:1908.
- [65] Harb, AJ, Tan, W, Wilding, GE, et al. Treating octogenarian and nonagenarian acute myeloid leukemia patients--predictive prognostic models. *Cancer* 2009; 115:2472.
- [66] Giles, FJ, Borthakur, G, Ravandi, F, et al. The haematopoietic cell transplantation comorbidity index score is predictive of early death and survival in patients over 60 years of age receiving induction therapy for acute myeloid leukaemia. *Br J Haematol* 2007; 136:624.
- [67] Sekeres, MA, Stone, RM, Zahrieh, D, et al. Decision-making and quality of life in older adults with acute myeloid leukemia or advanced myelodysplastic syndrome. *Leukemia* 2004; 18:809.
- [68] Rabbat, A, Chaoui, D, Montani, D, et al. Prognosis of patients with acute myeloid leukaemia admitted to intensive care. *Br J Haematol* 2005; 129:350.

- [69] Ferrara, F, Annunziata, M, Copia, C, et al. Therapeutic options and treatment results for patients over 75 years of age with acute myeloid leukemia. *Haematologica* 1998; 83:126.
- [70] Leoni, F, Ciolli, S, Nozzoli, C, et al. Idarubicin in induction treatment of acute myeloid leukemia in the elderly. *Haematologica* 1997; 82:13.
- [71] Juliusson, G, Höglund, M, Karlsson, K, et al. Increased remissions from one course for intermediate-dose cytosine arabinoside and idarubicin in elderly acute myeloid leukaemia when combined with cladribine. A randomized population-based phase II study. *Br J Haematol* 2003; 123:810.
- [72] Vey, N, Coso, D, Bardou, VJ, et al. The benefit of induction chemotherapy in patients age > or = 75 years. *Cancer* 2004; 101:325.
- [73] Gardin, C, Turlure, P, Fagot, T, et al. Postremission treatment of elderly patients with acute myeloid leukemia in first complete remission after intensive induction chemotherapy: results of the multicenter randomized Acute Leukemia French Association (ALFA) 9803 trial. *Blood* 2007; 109:5129.
- [74] British Committee for Standards in Haematology, Milligan, DW, Grimwade, D, et al. Guidelines on the management of acute myeloid leukaemia in adults. *Br J Haematol* 2006; 135:450.
- [75] Stone, RM. The difficult problem of acute myeloid leukemia in the older adult. *CA Cancer J Clin* 2002; 52:363.
- [76] Menzin, J, Lang, K, Earle, CC, et al. The outcomes and costs of acute myeloid leukemia among the elderly. *Arch Intern Med* 2002; 162:1597.
- [77] Leith, CP, Kopecky, KJ, Godwin, J, et al. Acute myeloid leukemia in the elderly: assessment of multidrug resistance (MDR1) and cytogenetics distinguishes biologic subgroups with remarkably distinct responses to standard chemotherapy. A Southwest Oncology Group study. *Blood* 1997; 89:3323.
- [78] Büchner, T, Berdel, WE, Haferlach, C, et al. Age-related risk profile and chemotherapy dose response in acute myeloid leukemia: a study by the German Acute Myeloid Leukemia Cooperative Group. *J Clin Oncol* 2009; 27:61.
- [79] Bow, EJ, Sutherland, JA, Kilpatrick, MG, et al. Therapy of untreated acute myeloid leukemia in the elderly: remission-induction using a non-cytarabine-containing regimen of mitoxantrone plus etoposide. *J Clin Oncol* 1996; 14:1345.
- [80] Letendre, L, Noel, P, Litzow, MR, et al. Treatment of acute myelogenous leukemia in the older patient with attenuated high-dose ara-C. *Am J Clin Oncol* 1998; 21:142.
- [81] Schoch, C, Kern, W, Krawitz, P, et al. Dependence of age-specific incidence of acute myeloid leukemia on karyotype. *Blood* 2001; 98:3500.
- [82] van der Holt, B, Breems, DA, Berna Beverloo, H, et al. Various distinctive cytogenetic abnormalities in patients with acute myeloid leukaemia aged 60 years and older express adverse prognostic value: results from a prospective clinical trial. *Br J Haematol* 2007; 136:96.
- [83] LeBeau, MM, Larson, RA. Cytogenetics and neoplasia. In: *Hematology Basic Principles and Practice*, 2nd ed, Hoffman, R, Benz, EJ Jr, Shattil, SJ, et al. (Eds), Churchill Livingstone, New York 1995.
- [84] Schiffer, CA, Lee, EJ, Tomiyasu, T, et al. Prognostic impact of cytogenetic abnormalities in patients with de novo acute nonlymphocytic leukemia. *Blood* 1989; 73:263.

- [85] Grimwade, D, Walker, H, Harrison, G, et al. The predictive value of hierarchical cytogenetic classification in older adults with acute myeloid leukemia (AML): analysis of 1065 patients entered into the United Kingdom Medical Research Council AML11 trial. *Blood* 2001; 98:1312.
- [86] Moorman, AV, Roman, E, Cartwright, RA, Morgan, GJ. Age-specific incidence rates for cytogenetically-defined subtypes of acute myeloid leukaemia. *Br J Cancer* 2002; 86:1061.
- [87] Rao, AV, Valk, PJ, Metzeler, KH, et al. Age-specific differences in oncogenic pathway dysregulation and anthracycline sensitivity in patients with acute myeloid leukemia. *J Clin Oncol* 2009; 27:5580.
- [88] Schiffer, CA, Dodge, R, Larson, RA. Long-term follow-up of Cancer and Leukemia Group B studies in acute myeloid leukemia. *Cancer* 1997; 80:2210.
- [89] Löwenberg, B, Zittoun, R, Kerkhofs, H, et al. On the value of intensive remission-induction chemotherapy in elderly patients of 65+ years with acute myeloid leukemia: a randomized phase III study of the European Organization for Research and Treatment of Cancer Leukemia Group. *J Clin Oncol* 1989; 7:1268.
- [90] Ferrara, F, Mirto, S, Zagonel, V, Pinto, A. Acute myeloid leukemia in the elderly: a critical review of therapeutic approaches and appraisal of results of therapy. *Leuk Lymphoma* 1998; 29:375.
- [91] Friedman, HD, Landaw, SA. Recent-onset myelodysplastic syndrome mimicking acute leukemia during infection. *Ann Hematol* 1996; 72:85.
- [92] Baudard, M, Marie, JP, Cadiou, M, et al. Acute myelogenous leukaemia in the elderly: retrospective study of 235 consecutive patients. *Br J Haematol* 1994; 86:82.
- [93] Goldstone, AH, Burnett, AK, Wheatley, K, et al. Attempts to improve treatment outcomes in acute myeloid leukemia (AML) in older patients: the results of the United Kingdom Medical Research Council AML11 trial. *Blood* 2001; 98:1302.
- [94] Mayer, RJ, Davis, RB, Schiffer, CA, et al. Intensive postremission chemotherapy in adults with acute myeloid leukemia. Cancer and Leukemia Group B. *N Engl J Med* 1994; 331:896.
- [95] Prébet, T, Boissel, N, Reutenauer, S, et al. Acute myeloid leukemia with translocation (8;21) or inversion (16) in elderly patients treated with conventional chemotherapy: a collaborative study of the French CBF-AML intergroup. *J Clin Oncol* 2009; 27:4747.
- [96] Fernandez, HF, Sun, Z, Yao, X, et al. Anthracycline dose intensification in acute myeloid leukemia. *N Engl J Med* 2009; 361:1249.
- [97] Burnett, AK, Milligan, D, Goldstone, A, et al. The impact of dose escalation and resistance modulation in older patients with acute myeloid leukaemia and high risk myelodysplastic syndrome: the results of the LRF AML14 trial. *Br J Haematol* 2009; 145:318.
- [98] Buchner, T, Berdel, WE, Haferlach, C, et al. Long-term results in patients with acute myeloid leukemia (AML): the influence of high-dose AraC, G-CSF priming, autologous transplantation, prolonged maintenance, age, history, cytogenetics, and mutation status. Data of the AMLCG 1999 Trial (abstract). *Blood* 2009; 114:200a.
- [99] Rowe, JM, Neuberg, D, Friedenber, W, et al. A phase 3 study of three induction regimens and of priming with GM-CSF in older adults with acute myeloid leukemia: a trial by the Eastern Cooperative Oncology Group. *Blood* 2004; 103:479.

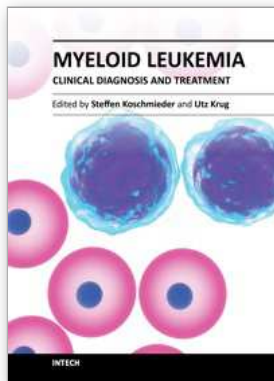
- [100] Godwin, JE, Kopecky, KJ, Head, DR, et al. A double-blind placebo-controlled trial of granulocyte colony-stimulating factor in elderly patients with previously untreated acute myeloid leukemia: a Southwest oncology group study (9031). *Blood* 1998; 91:3607.
- [101] Uyl-de Groot, CA, Löwenberg, B, Vellenga, E, et al. Cost-effectiveness and quality-of-life assessment of GM-CSF as an adjunct to intensive remission induction chemotherapy in elderly patients with acute myeloid leukemia. *Br J Haematol* 1998; 100:629.
- [102] Stone, RM, Berg, DT, George, SL, et al. Granulocyte-macrophage colony-stimulating factor after initial chemotherapy for elderly patients with primary acute myelogenous leukemia. *Cancer and Leukemia Group B. N Engl J Med* 1995; 332:1671.
- [103] Stone, RM, Berg, DT, George, SL, et al. Postremission therapy in older patients with de novo acute myeloid leukemia: a randomized trial comparing mitoxantrone and intermediate-dose cytarabine with standard-dose cytarabine. *Blood* 2001; 98:548.
- [104] Amadori, S, Suci, S, Jehn, U, et al. Use of glycosylated recombinant human G-CSF (lenograstim) during and/or after induction chemotherapy in patients 61 years of age and older with acute myeloid leukemia: final results of AML-13, a randomized phase-3 study. *Blood* 2005; 106:27.
- [105] Manoharan, A, Baker, RL, Kyle, PW. Low-dose combination chemotherapy for acute myeloid leukemia in elderly patients: a novel approach. *Am J Hematol* 1997; 55:115.
- [106] Feldman, EJ, Seiter, K, Damon, L, et al. A randomized trial of high- vs standard-dose mitoxantrone with cytarabine in elderly patients with acute myeloid leukemia. *Leukemia* 1997; 11:485.
- [107] Stein, RS, Vogler, WR, Winton, EF, et al. Therapy of acute myelogenous leukemia in patients over the age of 50: a randomized Southeastern Cancer Study Group trial. *Leuk Res* 1990; 14:895.
- [108] Estey, EH, Thall, PF, Giles, FJ, et al. Gemtuzumab ozogamicin with or without interleukin 11 in patients 65 years of age or older with untreated acute myeloid leukemia and high-risk myelodysplastic syndrome: comparison with idarubicin plus continuous-infusion, high-dose cytosine arabinoside. *Blood* 2002; 99:4343.
- [109] Anderson, JE, Kopecky, KJ, Willman, CL, et al. Outcome after induction chemotherapy for older patients with acute myeloid leukemia is not improved with mitoxantrone and etoposide compared to cytarabine and daunorubicin: a Southwest Oncology Group study. *Blood* 2002; 100:3869.
- [110] Giles, FJ, Kantarjian, HM, Cortes, JE, et al. Adaptive randomized study of idarubicin and cytarabine versus troxacitabine and cytarabine versus troxacitabine and idarubicin in untreated patients 50 years or older with adverse karyotype acute myeloid leukemia. *J Clin Oncol* 2003; 21:1722.
- [111] Ossenkoppele, GJ, Graveland, WJ, Sonneveld, P, et al. The value of fludarabine in addition to ARA-C and G-CSF in the treatment of patients with high-risk myelodysplastic syndromes and AML in elderly patients. *Blood* 2004; 103:2908.
- [112] Faderl, S, Verstovsek, S, Cortes, J, et al. Clofarabine and cytarabine combination as induction therapy for acute myeloid leukemia (AML) in patients 50 years of age or older. *Blood* 2006; 108:45.

- [113] Sudan, N, Rossetti, JM, Shaddock, RK, et al. Treatment of acute myelogenous leukemia with outpatient azacitidine. *Cancer* 2006; 107:1839.
- [114] Giles, F, Rizzieri, D, Karp, J, et al. Cloretazine (VNP40101M), a novel sulfonylhydrazine alkylating agent, in patients age 60 years or older with previously untreated acute myeloid leukemia. *J Clin Oncol* 2007; 25:25.
- [115] Lancet, JE, Gojo, I, Gotlib, J, et al. A phase 2 study of the farnesyltransferase inhibitor tipifarnib in poor-risk and elderly patients with previously untreated acute myelogenous leukemia. *Blood* 2007; 109:1387.
- [116] Clavio, M, Vignolo, L, Albarello, A, et al. Adding low-dose gemtuzumab ozogamicin to fludarabine, Ara-C and idarubicin (MY-FLAI) may improve disease-free and overall survival in elderly patients with non-M3 acute myeloid leukaemia: results of a prospective, pilot, multi-centre trial and comparison with a historical cohort of patients. *Br J Haematol* 2007; 138:186.
- [117] Soriano, AO, Yang, H, Faderl, S, et al. Safety and clinical activity of the combination of 5-azacytidine, valproic acid, and all-trans retinoic acid in acute myeloid leukemia and myelodysplastic syndrome. *Blood* 2007; 110:2302.
- [118] Faderl, S, Ravandi, F, Huang, X, et al. A randomized study of clofarabine versus clofarabine plus low-dose cytarabine as front-line therapy for patients aged 60 years and older with acute myeloid leukemia and high-risk myelodysplastic syndrome. *Blood* 2008; 112:1638.
- [119] Baer, MR, George, SL, Caligiuri, MA, et al. Low-dose interleukin-2 immunotherapy does not improve outcome of patients age 60 years and older with acute myeloid leukemia in first complete remission: Cancer and Leukemia Group B Study 9720. *J Clin Oncol* 2008; 26:4934.
- [120] Harousseau, JL, Martinelli, G, Jedrzejczak, WW, et al. A randomized phase 3 study of tipifarnib compared with best supportive care, including hydroxyurea, in the treatment of newly diagnosed acute myeloid leukemia in patients 70 years or older. *Blood* 2009; 121:1166.
- [121] Kantarjian, HM, Erba, HP, Claxton, D, et al. Phase II study of clofarabine monotherapy in previously untreated older adults with acute myeloid leukemia and unfavorable prognostic factors. *J Clin Oncol* 2010; 28:549.
- [122] Cashen, AF, Schiller, GJ, O'Donnell, MR, DiPersio, JF. Multicenter, phase II study of decitabine for the first-line treatment of older patients with acute myeloid leukemia. *J Clin Oncol* 2010; 28:556.
- [123] Fenaux, P, Mufti, GJ, Hellström-Lindberg, E, et al. Azacitidine prolongs overall survival compared with conventional care regimens in elderly patients with low bone marrow blast count acute myeloid leukemia. *J Clin Oncol* 2010; 28:562.
- [124] Fenaux, P, Mufti, GJ, Hellstrom-Lindberg, E, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. *Lancet Oncol* 2009; 10:223.
- [125] Blum, W, Klisovic, RB, Hackanson, B, et al. Phase I study of decitabine alone or in combination with valproic acid in acute myeloid leukemia. *J Clin Oncol* 2007; 25:3884.

- [126] Ravandi, F, Issa, JP, Garcia-Manero, G, et al. Superior outcome with hypomethylating therapy in patients with acute myeloid leukemia and high-risk myelodysplastic syndrome and chromosome 5 and 7 abnormalities. *Cancer* 2009; 115:5746.
- [127] Baer, MR, George, SL, Dodge, RK, et al. Phase 3 study of the multidrug resistance modulator PSC-833 in previously untreated patients 60 years of age and older with acute myeloid leukemia: Cancer and Leukemia Group B Study 9720. *Blood* 2002; 100:1224.
- [128] van der Holt, B, Löwenberg, B, Burnett, AK, et al. The value of the MDR1 reversal agent PSC-833 in addition to daunorubicin and cytarabine in the treatment of elderly patients with previously untreated acute myeloid leukemia (AML), in relation to MDR1 status at diagnosis. *Blood* 2005; 106:2646.
- [129] Fehniger, TA, Byrd, JC, Marcucci, G, et al. Single-agent lenalidomide induces complete remission of acute myeloid leukemia in patients with isolated trisomy 13. *Blood* 2009; 113:1002.
- [130] Vij, R, Nelson, A, Uy, GL, et al. A phase II study of high dose lenalidomide as initial therapy for acute myeloid leukemia in patients >60 years old (abstract). *Blood* 2009; 114:347.
- [131] Chauncey, TR, Gundacker, H, Shadman, M, et al. Sequential phase II Southwest Oncology Group studies (S0112 and S0301) of daunorubicin and cytarabine by continuous infusion, without and with ciclosporin, in older patients with previously untreated acute myeloid leukaemia. *Br J Haematol* 2010; 148:48.
- [132] Cassileth, PA, Harrington, DP, Hines, JD, et al. Maintenance chemotherapy prolongs remission duration in adult acute nonlymphocytic leukemia. *J Clin Oncol* 1988; 6:583.
- [133] Löwenberg, B, Beck, J, Graux, C, et al. Gemtuzumab ozogamicin as postremission treatment in AML at 60 years of age or more: results of a multicenter phase 3 study. *Blood* 2010; 115:2586.
- [134] Schiller, G, Lee, M. Long-term outcome of high-dose cytarabine-based consolidation chemotherapy for older patients with acute myelogenous leukemia. *Leuk Lymphoma* 1997; 25:111.
- [135] Wallen, H, Gooley, TA, Deeg, HJ, et al. Ablative allogeneic hematopoietic cell transplantation in adults 60 years of age and older. *J Clin Oncol* 2005; 23:3439.
- [136] Giralt, S, Ballen, K, Rizzo, D, et al. Reduced-intensity conditioning regimen workshop: defining the dose spectrum. Report of a workshop convened by the center for international blood and marrow transplant research. *Biol Blood Marrow Transplant* 2009; 15:367.
- [137] Champlin, R, Khouri, I, Shimoni, A, et al. Harnessing graft-versus-malignancy: non-myeloablative preparative regimens for allogeneic haematopoietic transplantation, an evolving strategy for adoptive immunotherapy. *Br J Haematol* 2000; 111:18.
- [138] Bertz, H, Potthoff, K, Finke, J. Allogeneic stem-cell transplantation from related and unrelated donors in older patients with myeloid leukemia. *J Clin Oncol* 2003; 21:1480.
- [139] Valcárcel, D, Martino, R, Caballero, D, et al. Sustained remissions of high-risk acute myeloid leukemia and myelodysplastic syndrome after reduced-intensity conditioning allogeneic hematopoietic transplantation: chronic graft-versus-host disease is the strongest factor improving survival. *J Clin Oncol* 2008; 26:577.

- [140] Gyurkocza, B, Storb, R, Storer, BE, et al. Nonmyeloablative allogeneic hematopoietic cell transplantation in patients with acute myeloid leukemia. *J Clin Oncol* 2010; 28:2859.
- [141] McClune, BL, Weisdorf, DJ, Pedersen, TL, et al. Effect of age on outcome of reduced-intensity hematopoietic cell transplantation for older patients with acute myeloid leukemia in first complete remission or with myelodysplastic syndrome. *J Clin Oncol* 2010; 28:1878.
- [142] Estey, E, de Lima, M, Tibes, R, et al. Prospective feasibility analysis of reduced-intensity conditioning (RIC) regimens for hematopoietic stem cell transplantation (HSCT) in elderly patients with acute myeloid leukemia (AML) and high-risk myelodysplastic syndrome (MDS). *Blood* 2007; 109:1395.
- [143] Hutchins, LF, Unger, JM, Crowley, JJ, et al. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. *N Engl J Med* 1999; 341:2061.
- [144] Mengis, C, Aebi, S, Tobler, A, et al. Assessment of differences in patient populations selected for excluded from participation in clinical phase III acute myelogenous leukemia trials. *J Clin Oncol* 2003; 21:3933.
- [145] Surveillance Epidemiology and End Results (SEER) Program. Limited use-data (1973–2004). National Cancer Institute D, Surveillance Research Program, Cancer Statistics Branch. SEER Web site. [http:// www.seer.cancer.gov](http://www.seer.cancer.gov). Accessed April 2007. *Haematologica*. 2008;93:594–600.
- [146] Juliusson G, Antunovic P, Derolf A, et al. Age and acute myeloid leukemia: real world data on decision to treat and outcomes from the Swedish Acute Leukemia Registry. *Blood*. 2009;113:4179–4187.
- [147] Pulte D, Gondos A, Brenner H, Pulte D, Gondos A, Brenner H. Improvements in survival of adults diagnosed with acute myeloblastic leukemia in the early 21st century.





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This book comprises a series of chapters from experts in the field of diagnosis and treatment of myeloid leukemias from all over the world, including America, Europe, Africa and Asia. It contains both reviews on clinical aspects of acute (AML) and chronic myeloid leukemias (CML) and original publications covering specific clinical aspects of these important diseases. Covering the specifics of myeloid leukemia epidemiology, diagnosis, risk stratification and management by authors from different parts of the world, this book will be of interest to experienced hematologists as well as physicians in training and students from all around the globe.

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