Published in final edited form as:

Leuk Res. 2012 April ; 36(4): 407–412. doi:10.1016/j.leukres.2011.12.019.

Are low-intensity induction strategies better for older patients with acute myeloid leukemia?

Gail J. Roboz^{a,*}, Usama Wissa^a, Ellen K. Ritchie^a, Usama Gergis^a, Sebastian Mayer^a, Joseph M. Scandura^a, Paul J. Christos^b, and Eric J. Feldman^a

^aLeukemia Program, Weill Medical College of Cornell University and the New York Presbyterian Hospital, New York, NY, United States

^bDivision of Biostatistics and Epidemiology, Department of Public Health, Weill Medical College of Cornell University, New York, NY, United States

Abstract

This study compares outcomes of low-intensity versus standard-intensity induction strategies for older patients with acute myeloid leukemia at the Weill Cornell Leukemia Program. From 1999 to 2009, 298 adults ≥ 60 years with AML underwent induction chemotherapy with low-intensity and standard-intensity regimens, based on physician and patient preferences and investigational protocol availability. Overall, 33% of the cohort achieved complete remission with initial treatment, 23% with low-intensity induction and 53% with standard-intensity induction ($P < 0.0001$). The median overall survival was 6.5 months and there was no significant difference in overall survival between patients initially treated with a low-intensity regimen compared to those receiving standard-intensity induction. There were no differences in 30- or 60-day mortality between the two groups.

Keywords

Leukemia; Acute; Myeloid; Drug therapy; Clinical trials; Aged; Remission induction

1. Introduction

The median age at diagnosis of acute myeloid leukemia (AML) is 67 years and approximately one-third of newly diagnosed patients are over 75 years old [1]. Most AML patients over 60 years die within a year of diagnosis and overall survival in this age group has not increased significantly during the last three decades. Several host- and disease-related factors contribute to the poor outcomes in older AML patients, including physical

© 2012 Elsevier Ltd. All rights reserved.

*Corresponding author at: Weill Medical College of Cornell University, the New York Presbyterian Hospital, 520 East 68th Street, New York, NY 10065, United States. Tel.: +1 212 746 6736; fax: +1 212 746 8246. gar2001@med.cornell.edu (G.J. Roboz).

Conflict of interest

The authors have no relevant conflicts of interest to disclose.

Authors' contributions: G.J.R. was involved in conception and design, writing, and final approval of the manuscript, as well as collection, assembly, analysis and interpretation of data. U.W. was involved in collection, assembly, analysis and interpretation of data; as well as writing and final approval of the manuscript. E.K.R. was involved in conception and design, and final approval of the manuscript; as well as collection, assembly, analysis and interpretation of data. U.G. was involved in writing and final approval of the manuscript; as well as collection and assembly of data. S.M. was involved in collection and assembly of data and final approval of the manuscript. J.M.S. was involved in collection and assembly of data, and final approval of the manuscript. P.J.C. was involved in analysis and interpretation of the data, writing, and final approval of the manuscript. E.J.F. was involved in conception and design, writing, and final approval of the manuscript.

frailty, medical comorbidities, increased incidence of antecedent hematologic disorders, higher frequency of adverse cytogenetics and increased p-glycoprotein expression [2]. In a retrospective analysis of 998 older patients treated with intensive remission induction therapy at the M.D. Anderson Cancer Center, multivariate analysis identified age >75 years, poor performance status, creatinine >1.3, unfavorable karyotype, duration of antecedent hematologic disorder >6 months, and treatment outside a laminar airflow room as adverse prognostic indicators. Patients with 3 or more of these factors had expected complete remission rates of <20%, 8-week mortality >50% and 1-year survival <10% [3]. Conversely, patients without adverse features by these criteria had an expected remission rate of >60% and 1-year survival >50% with intensive induction [3]. Older patients with core-binding factor leukemias or *NPM1* mutations have also been shown to have high remission rates and improved overall survival with intensive induction [4].

Based on these and other clinical and biologic features, older AML patients are generally offered one of four different treatment options: “standard” induction with infusional cytarabine and an anthracycline; “low-intensity” induction with low-dose cytarabine or, more recently, a hypomethylating agent; supportive care with hydrea, antibiotics and transfusions; or a clinical trial. More than 2 decades ago, a randomized trial of induction therapy with daunorubicin, vincristine and cytarabine versus supportive care with palliative, low-dose chemotherapy showed improved overall survival, albeit only by 10 weeks, for the intensively treated patients [5]. Importantly, the patients treated with supportive care did not seem to spend less time in the hospital or benefit from improved quality of life compared to those who received intensive induction. Recent registry data from 3000 unselected older AML patients in Sweden show improved rates of early death and long-term survival in intensively treated patients [6]. The paradigm of the low-intensity approach, low-dose cytarabine, has been used for decades in patients deemed unsuitable for intensive induction. In a large randomized trial, low-dose cytarabine resulted in complete remission in 18% of patients with a median overall survival of 575 days for patients who achieved remission [7]. Despite these data, older patients with AML are frequently offered only best supportive care and this practice is consistent with the current guidelines of the National Comprehensive Cancer Network (NCCN) [8,9]. Clinicians remain reluctant to subject elderly AML patients to what they believe is ineffective and toxic therapy.

The selection of which older AML patients are “fit” or “appropriate” for standard chemotherapy is a major clinical challenge and the subject of extensive clinical research. Because many older patients have multiple adverse prognostic features and are predicted to fare poorly with standard induction, there is an ongoing search for “low-intensity” strategies with the goal of improving outcomes compared to palliative approaches or low-dose ara-C, while minimizing the morbidity and mortality associated with traditional anthracycline and cytarabine-based regimens. From 1999 to 2009, the Leukemia Program at Weill Cornell Medical Center in New York City treated older AML patients with several different standard and investigational, low-intensity and intensive induction regimens. The objective of this analysis was to review these treatment approaches and compare outcomes of low-intensity versus intensive strategies at this institution.

2. Material and methods

From 1999 to 2009, 298 adults with AML >60 years underwent induction chemotherapy at Weill-Cornell Medical Center/The New York Presbyterian Hospital. Approval for retrospective chart review was granted by the Institutional Review Board of Weill Cornell Medical College and all 298 patients were included for analysis. Based on physician and patient preferences and/or investigational protocol availability, patients were treated with either a standard-intensity, cytarabine-based induction regimen, or an alternative, low-

intensity regimen. Standard-intensity regimens included: (1) cytarabine 100 mg/m² by 24-h continuous infusion × 7 days with daunorubicin 60 mg/m² IV daily × 3 days ± etoposide 100 mg/m² IV daily × 7 days and (2) cytarabine 100 mg/m² by 24-h continuous infusion × 7 days with gemtuzumab 6 mg/m² IV × 1 (investigational). Low-intensity regimens included: (1) cytarabine 10 mg/m² subcutaneously twice daily × 14 days; (2) cytarabine 10 mg/m² subcutaneously twice daily × 14 days with arsenic trioxide 0.25 mg/kg days 1–5 and 8–12 (investigational); (3) tipifarnib 600 mg/m² × 21 days (investigational); (4) tipifarnib 300–600 mg/m² × 14–21 days with etoposide 100–200 mg/m² orally days 1–3 and 7–10 (investigational). The details of the investigational protocols have been published previously [10–12].

Patients who failed to respond to or relapsed after initial therapy were offered a variety of low and standard-intensity salvage regimens, depending on their clinical status, preference and investigational protocol availability. Low-intensity salvage options included low-dose cytarabine, tipifarnib combined with etoposide (investigational), tipifarnib combined with low-dose cytarabine (investigational), arsenic trioxide combined with low-dose cytarabine, decitabine 20 mg/m² daily × 5 with gemtuzumab ozogamicin 3 mg/m² IV × 1, decitabine 20 mg/m² IV daily × 10 days, and investigational phase I agents including the anti-CD33 monoclonal antibody SGN-33 [13] and the multi-kinase inhibitor KW2449 [14]. Standard-intensity salvage options included cytarabine 100 mg/m² by continuous infusion for 7 days with either daunorubicin 60 mg/m² or the same dose and schedule of cytarabine combined with laromustine (formerly cloretazine) 300–600 mg/m² IV × 1 (investigational), an investigational liposomal combination of daunorubicin and cytarabine (CPX-351), gemtuzumab ozogamicin, and gemtuzumab ozogamicin combined with cytarabine.

Patients were treated at the New York Presbyterian Hospital Cornell Campus by the same group of clinicians. Care was administered per the standard algorithms of the Leukemia Program, including antibiotic and antifungal prophylaxis, treatment of neutropenia-related infections, use of hematopoietic growth factors, and transfusion support. Per institutional practice, patients receiving daunorubicin-containing regimens were required to have baseline left ventricular ejection fraction ≥ 50%. Patients on clinical trials for low-dose cytarabine with or without arsenic trioxide and the tipifarnib-based studies were required to have normal liver and renal function as per protocol and ECOG performance status of ≤ 2. Response criteria for all regimens were consistent with Cheson et al. [15].

Descriptive statistics (i.e., frequency, percent, median, range) for demographic and clinical characteristics were calculated for all patients in the cohort as well as stratified by type of intensity regimen (i.e., low-intensity vs. standard-intensity induction regimens). The chi-square test or the Wilcoxon rank-sum test was used, as appropriate, to compare demographic and clinical characteristics between patients receiving low-intensity induction regimens and patients receiving standard-intensity induction regimens. Overall survival (defined as the interval between the date of initial treatment and the date of last follow-up or death) was estimated by Kaplan–Meier survival analysis, and univariate associations between demographic/clinical variables and overall survival were assessed by the log-rank test. The independent effect of demographic/clinical predictors on overall survival was assessed by multivariate Cox proportional hazards regression analysis. Adjusted odds ratios were computed and 95% confidence intervals for the odds ratios and median overall survival time estimates are presented to assess the precision of the obtained estimates. Median follow-up time for the cohort of patients was computed based on survivors. All *P*-values are two-sided with statistical significance evaluated at the 0.05 alpha level. All analyses were performed in SAS Version 9.2 (SAS Institute, Inc., Cary, NC) and Stata Version 11.0 (StataCorp, College Station, TX).

3. Results

Clinical characteristics of the patients ($N = 298$) are presented in Table 1. The median age was 72 years (range 60–89), 47% had an antecedent hematologic disorder and 42% had an unfavorable karyotype using the criteria of the Cancer and Leukemia Group B. One hundred and three patients (35%) received standard intensity therapy: 71 received daunorubicin with cytarabine $\pm$ etoposide and 32 were treated with gemtuzumab + cytarabine. One hundred and ninety-five patients (65%) were treated on low-intensity regimens: 88 with low-dose cytarabine $\pm$ arsenic trioxide and 107 on tipifarnib-based regimens. A comparison of patients treated with standard induction regimens versus those receiving low-intensity therapy is shown in Table 2. Patients treated with low-intensity regimens were significantly older compared to those given standard induction (median age 75 years vs. 67 years, respectively, $P < 0.0001$) and had a higher percentage of unfavorable karyotype (46% vs. 33%, respectively, $P = 0.03$). However, patients treated with low-intensity regimens had a better ECOG performance status (ECOG scores of 0 or 1) compared to patients receiving standard induction (73% vs. 61%, respectively, $P = 0.04$).

Overall, 33% percent of the total cohort achieved a complete remission (CR) with initial treatment, 23% with low-intensity induction and 53% with standard-intensity induction ($P < 0.0001$). Among the patients treated with low-intensity induction, 48 patients who did not initially achieve CR received a salvage regimen and 23 patients who achieved CR but subsequently relapsed were treated with a salvage regimen. Thus, a total of 71 patients (36%) who were initially treated with a low-intensity regimen eventually received a salvage regimen (intensive salvage in 37 patients and low-intensity salvage in 34 patients). Of these 71 patients, 13 (18%) achieved first CR and 11 (15%) achieved second CR. Therefore, of the 195 patients initially treated with a low-intensity regimen, a total of 58 patients (30%) eventually achieved CR: 45 patients with initial CR, 8 with CR after standard-intensity salvage and 5 with CR after low-intensity salvage. A flow diagram of the 195 patients treated with initial low-intensity therapy is shown in Fig. 1.

Of the 98 patients who achieved complete remission, 90 received some type of post-remission therapy. Six patients (6%) were treated with high-dose cytarabine, 17 (17%) received 5 days of infusional cytarabine combined with 2 days of daunorubicin and the rest received a variety of lower-intensity consolidation strategies, including arsenic trioxide, tipifarnib, hypomethylating agents and 6-thioguanine, based on their clinical trial protocol or investigator preference. Sixteen patients (16%) underwent allogeneic stem cell transplantation in first remission.

The median overall survival for all 298 patients was 6.5 months (95% CI = 5.1–8.0 months). There was no significant difference in overall survival (OS) between patients initially treated with a low-intensity regimen (median OS = 5.9 months; 95% CI = 4.0–7.6 months) compared to those receiving standard-intensity induction (median OS = 7.7 months; 95% CI = 5.7–10.6 months; $P = 0.72$) (Fig. 2). Also, there were no differences in 30-day and 60-day mortality rates between the treatment groups. The 30-day mortality rate was 9.7% for patients initially treated with low-intensity therapy and 15.5% for those initially treated with standard-intensity induction ($P = 0.14$). Similarly, the 60-day mortality rate was 20.5% for patients initially treated with low-intensity therapy and 26.2% for patients initially treated with standard-intensity induction ($P = 0.26$) (Table 3).

Further evaluation of the relationship between induction strategy and overall survival among defined subsets of patients (i.e., patients >75 years of age [$N = 102$]; patients with an antecedent hematologic disorder [$N = 141$]; patients with unfavorable karyotype [$N = 124$]) still did not reveal any survival difference between the low-intensity and standard-intensity

induction strategies in these subsets by univariate analysis. Notably, however, the median overall survival for patients >75 years was only 4 months (95% CI = 3.0–6.0 months).

By multivariate analysis, male gender (adjusted hazard ratio (HR) = 1.40; $P = 0.01$), age over 75 (adjusted HR = 1.76; $P < 0.0001$), unfavorable karyotype (adjusted HR = 1.78; $P < 0.0001$), and ECOG performance status >2 (adjusted HR = 1.89; $P = 0.02$) were all associated with shorter overall survival. Conversely, complete remission status was significantly associated with improved overall survival (Fig. 3). Predictably, patients who responded to initial treatment had a much longer median overall survival than those who did not (17.9 months vs. 3.6 months, respectively, $P < 0.0001$) (Fig. 3). There was a small difference in overall survival favoring low-intensity induction when patients were stratified by initial treatment response (Figs. 4 and 5).

All patients required many in-patient and out-patient visits during their treatment. The number of days spent hospitalized as an in-patient and the number of days spent in the out-patient department was determined for each individual patient and then calculated as a percentage of the total days of survival, i.e. percent inpatient time = inpatient days/total survival days $\times 100\%$. The median value reported is the median percent time as an in-patient, out-patient, or both for the group of patients in question. Patients treated initially with a low-intensity regimen spent a median 26% of their survival time hospitalized as an in-patient and a median 5.9% of their survival time attending out-patient appointments. In comparison, patients initially treated with standard-intensity therapy spent a median 30% of their total survival time as an in-patient and a median 1.6% of their survival time as an out-patient. The total time spent as an in-patient was significantly greater for patients treated initially with a standard-intensity regimen, compared to those treated initially with a low-intensity regimen ($P < 0.01$), whereas the total time spent as an out-patient was significantly greater for the patients treated initially with a low-intensity regimen, compared to those treated initially with a standard-intensity regimen ($P < 0.0001$). However, there was no significant difference in the total time spent in a medical setting (in-patient combined with out-patient) between the two treatment groups: 34% for patients with initial low-intensity treatment and 38% for patients initially treated with a standard-intensity regimen ($P = 0.10$). Of note, patients who achieved CR at any time during their treatment spent a median of 23% of their survival time in a medical setting (in-patient combined with out-patient), compared to 54% for patients who did not respond to treatment ($P < 0.0001$).

4. Discussion

There is no universally accepted standard of care for older patients with AML because the patient population is clinically heterogeneous and currently available therapies are largely ineffective. During the last decade, the Weill Cornell/New York Presbyterian Hospital Leukemia Program has focused on clinical trials of novel agents for older patients with AML. Although the reported analysis is retrospective and non-randomized, it reflects a large clinical experience and is hoped to stimulate discussion that will guide clinical research in this challenging patient population.

The results confirm, unsurprisingly, that very few older AML patients have prolonged survival. More specifically, only a handful of patients who received initial treatment with any of the low-intensity regimens offered were long-term survivors after receiving only low-intensity therapy. Most patients either died of disease progression or failed to respond to their initial low-intensity treatments and went onto subsequent therapies, including the intensive regimens that they and their physicians were hoping to avoid. We were not surprised to find that the patients in our low-intensity group were significantly older and with worse cytogenetics than in the standard-intensity group, as our programmatic objective

was specifically to offer these poor-prognosis patients the opportunity to participate in clinical trials. It is important to note that patients initially treated with low-intensity induction actually had better performance status than those initially treated with standard-intensity induction. Thus, adverse biologic features were independent of performance status and more physically “fit” patients were not preferentially offered intensive induction strategies simply on the basis of performance status. In fact, it is definitely the case that whenever a clinical trial was available, patients with adverse cytogenetics were offered participation even if they were otherwise eligible for intensive induction. Still, the combination of better overall performance status and lower-intensity induction did not result in improved 30 and 60 day mortality rates compared to those treated with more intensive therapy.

Although the rate of CR was higher for intensively treated patients, overall survival was not different between the two groups. Other investigators have had different results. A European randomized trial between standard induction and low-dose chemotherapy and a case-control study from the Cleveland Clinic both showed improved survival with intensive induction [5,16]. This difference may have a few explanations, including (1) almost 20% of the patients in our cohort who were initially treated with low-intensity therapy eventually received standard induction and (2) not all low-intensity therapies are equal. Several of the regimens that we used, e.g. arsenic trioxide and low-dose ara-C, have been reported to have CR rates higher than with low-dose ara-C alone [10].

Unexpectedly, when stratified by response to initial treatment, the data show that low-intensity therapy resulted in modestly improved OS compared to standard induction both for patients who achieved remission (22.5 months vs. 15.1 months, $P = 0.04$) and for those who did not (3.9 months vs. 1.9 months, $P = 0.003$). However, it should be noted that comparisons between these specific response groups were not adjusted for other potentially confounding biologic, demographic and clinical factors. CR patients may have had a different baseline risk profile compared to failure patients. Thus, comparisons of low- vs.-standard-intensity treatment in these specific response groups are unadjusted and should be interpreted with caution. Also, among the original 195 patients treated with low-intensity induction, 13 patients achieved first CR and 11 achieved second CR after their initial induction treatment. This certainly had an impact on overall survival. Therefore, it is difficult to make any conclusions regarding the quality of the remissions induced by low versus standard-intensity induction.

Whether or not CR is required for prolonged survival has come into question based on data suggesting that the hypomethylating agent azacitidine prolongs survival in patients with high-risk myelodysplastic syndrome and smoldering AML despite producing a low CR rate of <20 [17]. The hypomethylating agent decitabine has shown promising CR rates as high as 47% in older AML patients, and recently demonstrated a survival benefit in a randomized trial versus supportive care [18,19]. In our evaluation, CR was clearly a requirement for prolonged survival.

While it is intuitive that not achieving CR may have a negative impact on quality of life and socioeconomic measures, i.e. more frequent physician visits, need for transfusions and antibiotics, persistent fatigue and/or depression, etc., these issues have been inadequately studied. We used an assessment of time spent in a medical setting, a combination of days spent as an out-patient and as a hospitalized in-patient, to try to gain some insight into how these patients spent their last few months of survival. It is not surprising that patients initially treated with a low-intensity regimen spent more days as an out-patient and those treated with a standard-intensity induction spent more days as an in-patient. However, it was a sobering finding that all the patients spent more than one-third of their remaining survival

in a medical setting. We found that being an out-patient was not necessarily “better” than being an in-patient. For example, although not formally reported, it was clear that many patients had significant struggles with issues such as transportation and organizing care-givers during their out-patient treatment. Many who could have been treated as out-patients from a medical perspective requested hospitalization for these reasons. It is also not known whether being an out-patient is “better” from a socioeconomic perspective; this topic clearly requires careful attention. Achievement of CR significantly reduced the total amount of time patients spent in a medical setting and it is likely that this, if studied prospectively, would translate into both quality of life and socioeconomic benefits. If CR improves both survival and quality of life, it will obviously need to remain the primary goal of AML therapy for older patients.

We have drawn several conclusions from the last decade of conducting clinical trials in older patients with AML.

1. So far, we have not identified an induction regimen obviously superior to classical “7 + 3”. It should be noted that this analysis covered a time period during which hypomethylating agents were not yet used routinely for AML induction at Cornell.
2. Primary resistance and disease relapse remain the major barriers to improved survival, not the tolerability of therapy. This concept also seems to be true in recent stem cell transplant literature suggesting that age is not the major determinant of outcome after transplantation [20].
3. It is feasible to administer novel treatment regimens to older patients with AML followed by standard-intensity treatments if remission is not obtained or lost.
4. The utility of the term “low-intensity” in the AML lexicon is unclear. Although the implication for patients and physicians is obviously that low-intensity treatment is in some way “easier”, how exactly it is easier and which treatments should be called “low-intensity” need to be clarified.
5. While it may be possible to administer certain regimens on an out-patient basis, older patients with AML still require significant follow-up and supportive care. The logistics of this type of care may be challenging and strongly depend on the facilities of the treatment center, as well as on the individual patient’s social circumstances.
6. It is clear that many older patients with AML can and do enter remission; more post-remission clinical trials are needed, especially using novel agents and stem cell transplantation strategies.
7. Clinical trials of older patients with AML must include quality of life and functional assessments.
8. Selection criteria for assigning patients to a standard-intensity or low-intensity approach should include a variety of clinical and biologic factors and have to be refined to include emerging molecular genetic subgroups.

Acknowledgments

The authors gratefully acknowledge funding support from Leukemia FightersTM. Dr. Paul Christos was partially supported by the following grant: Clinical Translational Science Center (CTSC) (UL1-RR024996). The sources of funding listed above had no involvement in study design, collection, or analysis and interpretation of data.

References

1. National Cancer Institute. [accessed 15.07.2011] Acute Myeloid Leukemia – Surveillance Epidemiology and End Results Stat Fact Sheets: Acute Myeloid Leukemia. <http://seer.cancer.gov/statfacts/html/amyl.html>
2. Appelbaum FR, Gundacker H, Head DR, Slovak ML, Willman CL, Godwin JE, et al. Age and acute myeloid leukemia. *Blood*. 2006; 107:3481–5. [PubMed: 16455952]
3. Kantarjian H, O'Brien S, Cortes J, Giles F, Faderl S, Jabbour E, 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; 106:1090–8. [PubMed: 16435386]
4. Marcucci G, Haferlach T, Dohner H. Molecular genetics of adult acute myeloid leukemia: prognostic and therapeutic implications. *J Clin Oncol*. 2011; 29:475–86. [PubMed: 21220609]
5. Lowenberg B, Zittoun R, Kerkhofs H, Jehn U, Abels J, Debusscher L, 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; 7:1268–74. [PubMed: 2475589]
6. Juliusson G, Antunovic P, Derolf A, Lehmann S, Mollgard L, Stockelberg D, et al. Age and acute myeloid leukemia: real world data on decision to treat and outcomes from the Swedish Acute Leukemia Registry. *Blood*. 2009; 113:4179–87. [PubMed: 19008455]
7. Burnett AK, Milligan D, Prentice AG, Goldstone AH, McMullin MF, Hills RK, 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; 109:1114–24. [PubMed: 17315155]
8. Menzin J, Lang K, Earle CC, Kerney D, Mallick R. The outcomes and costs of acute myeloid leukemia among the elderly. *Arch Intern Med*. 2002; 162:1597–603. [PubMed: 12123403]
9. National Comprehensive Cancer Network. Clinical practice guidelines in oncology – acute myeloid Leukemia. Version 2.2011. 2011.
10. Roboz GJ, Ritchie EK, Curcio T, Provenzano J, Carlin R, Samuel M, et al. Arsenic trioxide and low-dose cytarabine in older patients with untreated acute myeloid leukemia, excluding acute promyelocytic leukemia. *Cancer*. 2008; 113:2504–11. [PubMed: 18825661]
11. Karp JE, Flatten K, Feldman EJ, Greer JM, Loegering DA, Ricklis RM, et al. Active oral regimen for elderly adults with newly diagnosed acute myelogenous leukemia: a preclinical and phase 1 trial of the farnesyltransferase inhibitor tipifarnib (R115777, Zarnestra) combined with etoposide. *Blood*. 2009; 113:4841–52. [PubMed: 19109557]
12. Lancet JE, Gojo I, Gotlib J, Feldman EJ, Greer J, Liesveld JL, 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; 109:1387–94. [PubMed: 17082323]
13. Raza A, Jurcic JG, Roboz GJ, Maris M, Stephenson JJ, Wood BL, et al. Complete remissions observed in acute myeloid leukemia following prolonged exposure to lintuzumab: a phase 1 trial. *Leuk Lymphoma*. 2009; 50:1336–44. [PubMed: 19557623]
14. Pratz KW, Cortes J, Roboz GJ, Rao N, Arowojolu O, Stine A, et al. A pharmacodynamic study of the FLT3 inhibitor KW-2449 yields insight into the basis for clinical response. *Blood*. 2009; 113:3938–46. [PubMed: 19029442]
15. Cheson BD, Bennett JM, Kopecky KJ, Buchner T, Willman CL, Estey EH, et al. Revised recommendations of the international working group for diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in acute myeloid leukemia. *J Clin Oncol*. 2003; 21:4642–9. [PubMed: 14673054]
16. Baz R, Rodriguez C, Fu AZ, Jawde RA, Kalaycio M, Advani A, et al. Impact of remission induction chemotherapy on survival in older adults with acute myeloid leukemia. *Cancer*. 2007; 110:1752–9. [PubMed: 17724726]
17. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, Santini V, Gattermann N, Germing U, 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*. 2009; 28:562–9. [PubMed: 20026804]
18. Blum W, Garzon R, Klisovic RB, Schwind S, Walker A, Geyer S, 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 USA*. 2010; 107:7473–8. [PubMed: 20368434]
 19. Thomas XG, Dmoszynska A, Wierzbowska A, Kuliczowski K, Mayer J, Shelekhova T, et al. Results from a randomized phase III trial of decitabine versus supportive care or low-dose cytarabine for the treatment of older patients with newly diagnosed AML. *J Clin Oncol*. 2011
 20. McClune BL, Weisdorf DJ, Pedersen TL, Tunes da Silva G, Tallman MS, Sierra J, 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; 28:1878–87. [PubMed: 20212255]

Fig. 1.
Flow diagram of 195 patients treated with initial low-intensity therapy.

Fig. 2.

Overall survival by treatment intensity. Standard-intensity ($N = 103$ patients, 90 deaths): median overall survival = 7.7 months (95% CI = 5.7–10.6). Low-intensity ($N = 195$ patients, 163 deaths): median overall survival = 5.9 months (95% CI = 4.0–7.6).

Fig. 3. Overall survival by response to initial treatment. Failure ($N = 200$ patients, 186 deaths): median overall survival = 3.6 months (95% CI = 2.7–4.1). Complete remission ($N = 98$ patients, 67 deaths): median overall survival = 17.9 months (95% CI = 14.3–22.0).

Fig. 4.

Overall survival by treatment intensity (complete remission, $N = 98$). Standard-intensity ($N = 54$ patients, 42 deaths) (solid line): median OS = 15.1 months (95% CI = 11.7–19.6). Low-intensity ($N = 44$ patients, 25 deaths) (dotted line): median OS = 22.5 months (95% CI = 12.2–33.1).

Fig. 5. Overall survival by treatment intensity (failures, $N = 200$). Standard-intensity ($N = 49$ patients, 48 deaths) (solid line): median OS = 1.9 months (95% CI = 1.1–4.1). Low-intensity ($N = 151$ patients, 138 deaths) (dotted line): median OS = 3.9 months (95% CI = 2.9–4.5).

Table 1

Clinical characteristics.

Clinical characteristics	<i>N</i>
Total #	298
M/F	166/132
Median age (range)	72 (60–89)
ECOG PFS (range) ^a	1 (0–4)
0	56 (19%)
1	148 (50%)
2	76 (26%)
3	17 (6%)
4	1 (0.3%)
Unfavorable karyotype	124 (42%)
Prior hematologic disorder (MDS/MPD)	141 (47%)
Low-intensity Rx ^b	195 (65%)
Standard-intensity Rx ^c	103 (35%)

^aEastern cooperative oncology group performance status.^bLow-intensity: cytarabine ± arsenic trioxide and tipifarnib ± etoposide, see dosing details in text.^cStandard-intensity: daunorubicin/cytarabine and gemtuzumab/cytarabine, see dosing details in text.

Table 2

Differences in clinical characteristics by treatment group.

Variable	Low-intensity Rx	Standard-intensity Rx	P value
Total #	195	103	—
Median age	75	67	0.0001
M/F	103/92	63/40	0.17
AHD	47%	47.5%	0.86
Unfavorable karyotype	46%	33%	0.03

Table 3

Outcomes of low-intensity vs. standard-intensity induction.

	Low-intensity Rx	Standard-intensity Rx	P value
Total #	195	103	–
CR (%)	23%	53%	<0.0001
<30 day mortality	9.7%	15.5%	0.14
<60 day mortality	20.5%	26.2%	0.26