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# Less Intensive Therapy For Older Aml Patients

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# Less intensive therapy for older AML patients

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**Abstract**

LESS INTENSIVE THERAPY FOR OLDER AML PATIENTS. W. Thomas Clarke, Peter W. Marks, and Nikolai A. Podoltsev. Section of Hematology, Department of Internal Medicine, Yale University School of Medicine, New Haven, CT.

**Specific aims:** This single-center, retrospective study compared overall survival and hospitalization in older patients with acute myeloid leukemia (AML) receiving first-line treatment with standard induction chemotherapy and decitabine therapy.

**Methods:** Between January 2000 and December 2009, 36 patients at Yale-New Haven Hospital age 65 years and older with newly diagnosed AML received standard induction chemotherapy (n=11), decitabine therapy (n=11), or supportive care only (n=14). Data obtained included baseline characteristics, achievement of remission, overall survival, inpatient and outpatient visits, and early death.

**Results:** When compared to standard induction chemotherapy, decitabine patients were significantly older (77 vs 69 years, $P = .020$) yet had a favorable but nonsignificant trend for increased overall survival (9 vs 7 months, $P = .192$) and spent significantly fewer days in the hospital (30 vs 41 days, $P = .047$). Supportive care patients were older (84.5 years) and had a median survival of only 0.6 months.

**Conclusions:** Compared to standard induction chemotherapy, decitabine as first-line therapy for AML in older patients reduced hospitalization and had a similar overall survival.

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## INTRODUCTION

Leukemia is a cancer of the blood and bone marrow. Classification is first made into acute or chronic forms of the disease. Acute leukemias are characterized by a rapid increase in the number of neoplastic, immature bone marrow cells. Chronic leukemias are characterized by a slower accumulation of relatively more mature neoplastic blood cells. Further classification is made based on the affected cell type. In lymphocytic leukemias, the cancer arises in cells destined to become lymphocytes. In myelogenous leukemias, the cancer occurs in precursor cells destined to become red blood cells, platelets, neutrophils, monocytes, and some other types of white cells.

In acute myeloid leukemia (AML), non-functional neoplastic cells replace the normal blood cell precursors in the bone marrow. A deficiency of white blood cells makes patients susceptible to infection. Anemia, a reduction in red blood cells, causes fatigue. Thrombocytopenia, an abnormally low platelet count, results in bleeding or easy bruising (1). Other related symptoms include fevers with night sweats, loss of appetite, enlarged liver or spleen, and bone or joint pain. Leukemic cells may infiltrate skin and other organs and cause hyperviscosity and disseminated intravascular coagulation (DIC) (2).

### Epidemiology

In 2012, it is estimated that 13,780 people in the United States will be diagnosed with AML. In the same year, 10,200 people will die of the disease. The age-adjusted

incidence and death rates were 3.6 and 2.8, respectively, per 100,000 men and women per year. The median age at diagnosis is 66 years and the median age at death 72 years (3). AML has a peak incidence in the 80-84 year old age range (4). Men are more likely than women to be diagnosed with (4.3 versus 3.0 per 100,000) and die from (3.7 versus 2.2 per 100,000) AML. By race, whites have the highest incidence rate and death rate. The overall five-year survival rate between 2002 and 2008, the most recent available data, was 23.4% (3).

**Classification**

AML is a heterogeneous disorder that is classified by two systems, the newer World Health Organization (WHO) system and the older French-American-British (FAB) system. The WHO classification is based on common cytogenetic and molecular genetic abnormalities and is important for both treatment and prognosis. The WHO subtypes of AML include: AML with recurrent genetic abnormalities; AML with myelodysplasia-related changes; therapy related myeloid neoplasms; AML, not otherwise specified (NOS); myeloid sarcoma; myeloid proliferations related to Down syndrome; blastic plasmacytoid dendritic cell neoplasm; and acute leukemias of ambiguous lineage (5,6). The FAB system, initially proposed in 1976, is rarely used today and relies on older morphologic, cytochemical, and immunophenotypic features of neoplastic cells (7).

The first WHO subgroup, AML with recurrent genetic abnormalities, includes patients with one of many well-defined genetic abnormalities of prognostic

significance. Nearly 30% of AML patients are included in this group. Some examples of these genetic abnormalities include: t(15;17); t(8;21); and inv(16) (5). AML associated with these abnormalities are notable for having a favorable response to treatment (8).

The second WHO subgroup, AML with myelodysplasia-related changes, includes patients with a documented history of myelodysplastic syndrome (MDS) or a myeloproliferative neoplasm who evolve to AML with a marrow or blood blast count of greater than 20%. The subgroup also includes patients without such a history that meet one of two specific criteria. In the first criteria, 50% or more of the cells in two or more myeloid lineages are dysplastic (6). In the second criteria, the neoplastic cells must demonstrate specific MDS-related cytogenetic abnormalities (9). The incidence of AML with myelodysplasia-related changes is higher in elderly populations (10) and has been independently shown to be associated with lower rates of complete remission (11).

Therapy-related myeloid neoplasms, the third subgroup, includes patients with a history of chemotherapy and/or radiation who subsequently develop AML or MDS. Topoisomerase II inhibitor-related AML has a short latency period, ranging from six months to five years, characteristic translocations, and poor overall survival (12). Alkylating agent/radiation-related AML has a longer latency period ranging from four to seven years and is notable for a high incidence of abnormalities in chromosomes 5 and 7 (13). However, many patients have received treatment with

both topoisomerase II targeting drugs and alkylating agents, so dividing this subgroup by previous therapy is often not possible (6).

The remaining WHO subgroups provide a specific framework for patients that do not fit into one of the three previously mentioned most common subgroups (5).

**Myelodysplastic syndrome and myeloproliferative neoplasm**

MDS and myeloproliferative neoplasm are also clonal bone marrow disorders of the myeloid cell line. While distinct entities from AML, both MDS and MPN have the potential to transform into AML; one-third of MDS cases transforms to AML (14). The WHO and FAB classifications have different criteria for the diagnosis of AML and MDS. The WHO classification for AML requires leukemic myeloblasts constitute more than 20% of the blood or bone marrow cells (15) while the older FAB classification requires at least 30% (7). There exists a strong correlation between age and MDS diagnoses; patients over age 70 have an incidence rate of MDS nearly three times greater than of AML (10).

Myeloproliferative neoplasms are a group of hematologic neoplasms separated into two distinct groups based on the presence or absence of the Philadelphia chromosome. Chronic myelogenous leukemia (CML) carries the t(9;22) BCR-ABL translocation Philadelphia chromosome. Philadelphia chromosome negative MPNs include primary myelofibrosis, polycythemia vera, and essential thrombocytopenia. With current treatments, life expectancy is near normal in the majority of patients

with CML, polycythemia vera, and essential thrombocytopenia (16). Current treatments are inadequate for primary myelofibrosis, and life expectancy is reduced (17).

**Prognostic factors**

There are many factors that contribute to prognosis and treatment decisions in patients with newly diagnosed AML. These include age, performance status, WHO classification, karyotype, and molecular studies.

*Age*

Increasing age is a poor prognostic factor in AML across all age groups. In a study of 1181 patients under 30 years, 5-year event free survival was 54% in children less than 13 years, 46% in adolescents between 13 and 18 years, and 28% in young adults between 18 and 30 years (18). In a Swedish study of 2767 adults with AML, older patients fared worse in every measurable category. They were more likely to have a poor performance status and less likely to be fit for intensive chemotherapy. They had a higher rate of early death (defined as within 30 days of initial remission induction): 4% in patients less than 50 years, 14% in patients 65 through 69 years old, and 40% in patients over 85 years. Older patients had lower median overall survival: 1119 days in patients 16 through 55 years compared with 80 days in patients 76 through 89 years old (4). In another large study of adults, patients younger than 56 years old achieved complete response in 64% of cases compared to

33% of patients older than 75 years. Median disease-free survival was nearly 2.5 times greater in patients younger than 56 years than those older than 75 years (19).

Not surprisingly, performance status declines with age. Excellent performance status was found in a lower percentage of patients as age increased, from 35% in those less than 56 years old to 18% in those older than 75 years (19). Older patients are more likely to have chronic diseases including diabetes and renal, cardiac, and hepatic disorders. These chronic diseases make patients less able to tolerate chemotherapy. Furthermore, older patients have reduced bone marrow regenerative capacity following chemotherapy (20). However, studies show that age and performance status are each independent risk factors in AML. In one study, patients less than 56 years of age and over 75 years of age with the same moderate performance status were compared. In the younger group, 2% suffered an early death. In the older group, 64% had an early death (19).

*Cytogenetics*

It is well established that diagnostic cytogenetics is one of the most powerful prognostic indicators in AML (21,22). The Cancer and Leukemia Group B (CALGB) devised risk groups to predict success of induction chemotherapy and overall survival. Karyotypes including t(8;21), t(15,17), t(16;16), and inv(16) are known to confer a significantly better prognosis than other karyotypes, and patients with these karyotypes are in the CALGB "favorable" cytogenetic risk group (22,23).

The CALGB “intermediate” cytogenetic risk group includes over a dozen specific karyotypes including normal karyotypes, -Y, t(9,11), del(5q), +11, +13. The “adverse” risk group includes patients with complex karyotypes, defined by three or more abnormalities. Complex karyotypes are seen in 10-12% of AML cases (24). Additional CALGB “adverse” abnormalities includes inv(3), t(3;3), and -7 (22,23). Other groups have documented additional poor prognosis karyotypes including −5, del(5q), and −7 (25). A separate large study divided patients into two groups: cytogenetically normal or good prognosis karyotype versus poor prognosis karyotype. In the normal or good group, median survival was 90 weeks compared to 40 weeks in the negative karyotype group. Survival at 2 years was also significantly better in the normal or good group, 46% versus 20% in the poor group (26).

While there are believed to be biological differences between pediatric and adult AML, the reasons for the differences are largely unknown. Age is strongly associated with abnormal karyotypes in AML. In several large studies including thousands of patients, 55% of adults and 76% of children with AML were found to have abnormal karyotypes (21). It is well established that some chromosomal abnormalities are linked to particular ages. For example, 11q23 rearrangements are detected in 43-58% of infants aged twelve months or less (27) while this rearrangement is found in 5% of adults with AML aged 15-34 and 1% of patients older than 55 years (28).

The cytogenetic abnormalities more commonly found in older patients are more likely to indicate poor prognosis (29). A study of 968 adult patients demonstrated

younger patients had more favorable karyotypes. Cytogenetic risk was classified into favorable, intermediate and unfavorable categories. In patients younger than 56 years, 16% had a favorable karyotype and 33% had an unfavorable karyotype. However, in patients older than 75 years, only 4% had a favorable karyotype while 50% had an unfavorable karyotype (19).

*Genetic mutations*

As with cytogenetics, genetic mutations have significant prognostic value. The 45% of AML patients with normal cytogenetics was found to have divergent outcomes. Whole exome sequencing identified recurrent gene mutations and has become important in predicting clinical outcomes in this group that is cytogenetically normal but heterogeneous at the molecular level. For example, patients with an internal tandem duplication of the *FLT3* gene have a worse prognosis (30,31). Yet patients with the NPM1 mutation (32), DNMT3A mutation, and CEBPA biallelic mutations have higher rates of complete remission and overall survival (6,31). The European LeukemiaNet standard reporting system categorizes patients using cytogenetic analysis and mutation analyses of the NPM1, CEBPA, and FLT3 genes. The resulting groups are favorable, intermediate-I, intermediate-II, and adverse (6).

New technology in gene expression profiling is attempting for further classify AML and predict prognosis but at this time is only experimental and not used in a clinical setting. Many groups are using microarrays on large numbers of AML patients to further understand gene expression signatures (33-35). For example, using

microarray, one group was able to separate cytogenetically normal patients into two subgroups based on morphology and *FLT3* mutations. These subgroups were found to be strongly independent prognostic factors (36). Similarly, groups are using microRNA expression profiles for classification and prognostic purposes (37-39).

*Response to chemotherapy*

Response to chemotherapy represents an additional prognostic factor in older AML patients. Some of the reasons for therapeutic resistance are noted above, such as adverse cytogenetics, AML with myelodysplasia-related changes subtype and reduced performance status. Yet another factor is the presence of the multidrug resistance glycoprotein MDR1 that encodes a transmembrane efflux pump. This pump removes chemotherapeutic compounds such as anthracyclines from leukemic cells and is associated with poorer outcomes (40,41). Older patients have the highest rates of intrinsic drug resistance; in one study, 71% were found to have MDR1 protein expression and 58% were found to have functional drug efflux (11). Elderly patients without MDR1 had a complete remission rate of 68% versus 32% in those with MDR1 (11).

**Treatment**

Chemotherapy with the goal of inducing remission is typically recommended in all otherwise healthy older adults, as AML patients who achieve remission have been shown to have improved long-term survival and quality of life compared with those who receive only palliative therapy (4). Improved quality of life for those achieving

remission includes fewer hospitalizations, transfusions, and courses of antibiotics (4). Furthermore, relapse is unlikely in patients of any age who achieve and maintain complete remission for 3-4 years (42).

*Standard induction chemotherapy*

The current standard for induction chemotherapy in elderly patients is seven days of continuous infusion of the antimetabolic agent cytarabine plus three days of an anthracycline such as idarubicin or daunorubicin (43). As with any patient population, it is necessary to balance response and toxicity for chemotherapy dosing regimens. In older patients with AML this is especially difficult as the disease is more resistant to therapy yet the patients are more susceptible to the toxicities (44).

A recent study of AML patients between the ages of 60 and 83 demonstrated that doubling the dosage of daunorubicin from the previous conventional dose had higher rates of remission after the first cycle (52% versus 35%), higher rates of complete remission (73% versus 51%) and overall survival (38% versus 23%). Furthermore, the toxicity profiles of the conventional and double doses were similar (43). However, other studies have failed to support higher doses of chemotherapy. In another study of patients over age 60, dosages of daunorubicin and cytarabine were increased and a fourth course of treatment was added. Complete remission was observed in 54% of patients and no survival benefit was observed by increasing dosages or treatments. Only increased mortality was observed among patients receiving the multi-drug resistance modulator valspodar (PSC-833) (45).

Due to the significant toxicities of induction chemotherapy, supportive care is typically recommended in older patients with severe comorbidities, high risk disease and indolent disease (4,46,47). This leaves 64% of patients over the age of 65 with AML who are not treated and have a median survival of only 1.7 months (48).

*Low intensity treatment*

Compared to full strength induction treatment, low intensity treatment reduces the chance of obtaining complete remission, often resulting in reduced survival times (49). In one study, 87 patients over age 65 with AML were randomly assigned to receive low dose cytarabine or intensive chemotherapy. Patients in the intensive group were more likely to achieve complete remission but also more likely to have infectious complications, longer hospital stays and early death. In this study, there was no significant difference in overall survival (44). For many patients, low intensity treatment is the only option. Efforts have been made to risk-stratify patients and administer low-dose therapy to spare those with a low probability of survival benefit from toxic treatment. Unfortunately, most studies have been disappointing in improving overall survival (50). One trial of 217 patients unfit for intensive chemotherapy were randomized to receive either low-dose cytarabine or hydroxyurea. Patients in the low dose cytarabine group had a higher rate of complete remission (18% versus 1%) with similar toxicity profiles. Yet in both groups the median overall survival was less than six months (51).

Clinical trials are ongoing with newer chemotherapeutic agents including cloretazine (52), farnesyl transferase inhibitors, clofarabine and lenalidomide (53). The antineoplastic agent mitoxantrone in combination with cytarabine as well as the combination of daunorubicin, cytarabine, and etoposide were both found to be inferior to the combination of daunorubicin, cytarabine, and thioguanine (54). Other unsuccessful trials used the tyrosine kinase inhibitor imatinib (55) and the P-glycoprotein modulators valspodar and zosuquidar (56,57). The conjugated anti-CD33 antibody gemtuzumab ozogamicin was approved for the treatment of elderly patients with relapsed AML (58) and demonstrated effectiveness as a first line therapy in elderly patients (59). However, it has since been withdrawn from the market due to high levels of hepatic toxicity (60).

**Hypomethylating agents**

Drugs used in the treatment of MDS have been trialed in patients with AML with promising results. Azacitidine and decitabine are nucleoside analogues that incorporate into DNA and RNA and also inhibit DNA methyltransferase. By inhibiting methylation, these drugs are able to re-activate genes, notably tumor suppressor genes silenced by DNA hypermethylation (61). Azacitidine and decitabine are thereby able to have a dual effect: at low levels they induce differentiation in AML cells while at high doses they trigger apoptosis via DNA synthesis arrest (62). Azacitidine was found to increase overall survival in patients with higher-risk MDS or AML when compared to conventional regimens (63).

Outcomes equivalent to standard chemotherapy have been observed with decitabine in patients who are not candidates for aggressive therapy (64).

A Phase I study in 2004 demonstrated that decitabine was more effective at lower doses, the optimal being 15mg/$m^2$ intravenously over one hour daily, 5 days a week, for a total of two weeks (65). Early studies using a range of low dose decitabine regimens demonstrated overall response rates of 17% to 44% in patients with AML and MDS (65-68). A study of 95 patients with MDS and chronic myelomonocytic leukemia used three decitabine regimens: 20 mg/$m^2$ intravenously daily for 5 days; 20 mg/$m^2$ subcutaneously daily for 5 days; and 10 mg/$m^2$ intravenously daily for 10 days. The high dose intravenous schedule had the highest complete response rate of 39%, compared with 21% in the subcutaneous group and 24% in the 10 day group (69).

**Decitabine in older patients**

In 2010, results were published from the first study of older AML patients using decitabine as a first-line treatment. This multicenter phase II study enrolled 55 patients over the age of 60 years with a median age of 74 years. The patient profile was high-risk, as would be expected of older patients; 45% had poor risk cytogenetics and 35% had AML transformed from MDS. The treatment regimen was decitabine 20mg/$m^2$ intravenously for five days every four weeks. Patients were treated with a median three cycles of decitabine treatment, and 64% of patients received three or more cycles. The overall complete response rate was 25%,

including 20% in patients with poor risk cytogenetics and 21% in patients with a prior history of MDS. An additional 29% of patients who did not achieve CR maintained stable or improved bone marrow blast counts through a median five cycles of therapy. At least one serious adverse event was experienced by 47% of patients, with the most serious toxicities being myelosuppression, febrile neutropenia, and fatigue. The overall median survival was 7.7 months (70).

Further studies have demonstrated favorable results with the use of decitabine in older patients. Patients over the age of 60 with previously untreated AML who refused or were not candidates for intensive chemotherapy received low-dose decitabine using a previously untested ten-day therapy schedule. With 53 patients enrolled, 47% achieved a complete remission and an additional 17% achieved a morphologic leukemia-free state with incomplete count recovery. Median overall survival for all patients was 55 weeks. This study also investigated the relationship between clinical response with decitabine and pretreatment levels of *miR-29b*, a microRNA known to target DNA methyltransferase. Of the 23 patients with available pretreatment samples, a statistically significant association was made between those who responded to decitabine treatment and higher pretreatment levels of *miR-29b*. It is theorized that higher levels of *miR-29b* lead to a lower pre-treatment level of DNA methyltransferase and increased sensitivity to decitabine's hypomethylating effects (71).

Two large studies published in 2012 examined decitabine in older AML patients. In

a multicenter, randomized, open-label phase III trial of 485 patients, decitabine improved response rates (17.8% versus 7.8%) and overall survival (7.7 months versus 5.0 months) when compared to a treatment choice group receiving supportive care or cytarabine (72). A retrospective study of 671 patients compared intensive thermotherapy with azacitidine or decitabine therapy. The complete response rate was superior in the intensive chemotherapy group (42% versus 28%) but the median survival was equivalent (6.7 months versus 6.5 months). Multivariate analysis demonstrated age, cytogenetics and performance status but not type of therapy as independent prognostic factors. Notably, decitabine was associated with improved median survival when compared with azacitidine (8.8 months versus 5.5 months) (73).

Older patients with AML present unique challenges; both the disease and the health of the patient are different than that of younger patients. Older AML patients have forms of the disease that carry a worse prognosis such as poor risk cytogenetics and a history of MDS. Older patients also have inferior functional status and are less able to tolerate intensive chemotherapy. Too many older AML patients never undergo chemotherapy and those that do have poor rates of complete remission and short survival times. Better therapies for older AML patients are needed; trials using different dosing schedules and new drugs aimed specifically at this population group are ongoing.

**STATEMENT OF PURPOSE SPECIFIC HYPOTHESIS AND SPECIFIC AIMS OF THE THESIS**

Overall survival in older patients with AML is poor, so improving quality of life in this patient population is an important goal. It is hypothesized that in older patients with AML the reduced intensity chemotherapeutic agent decitabine is superior to standard induction chemotherapy or supportive care only.

The aim of this study is to determine whether improved quality of life can be achieved in older patients with AML using reduced intensity chemotherapy. Surrogates for quality of life include number of days spent in the hospital and number of outpatient visits. Other metrics by which to measure the effectiveness of the chemotherapeutic agents include overall survival, achievement of complete remission, and early death.

## METHODS

### Study Approval

A request for approval of medical record review was made with the Yale University Human Investigation Committee (HIC). The projected aim of the study was to compare the treatment of a group of individuals 65 years or older with AML treated with the hypomethylating agents 5-azacitidine or decitabine with a control group of individuals with AML treated with other chemotherapeutic agents. Outcomes to be measured included hospitalizations, outpatient visits, and overall survival. Records were requested from Yale-New Haven Hospital (YNHH) and Yale Cancer Center of all patients, both inpatient and outpatient, age 65 and older treated for AML (diagnosis codes 205.00 and 205.01) from January 1, 2000 through December 31, 2009. Electronic records to be interrogated included the admission/discharge database, Sunrise Clinical Manager, and Centricity. Data requested included diagnosis codes, medical record number and age. The study was given HIC protocol # 1006006963. The project was determined to be exempt from HIC review, as it involved the collection and study of existing data and records and was to be recorded in such a manner in which subjects cannot be identified, directly or through identifiers linked to the subjects.

### Patient Selection

Inclusion criteria were patients age 65 years of older with primary diagnosis of AML who received first line treatment with decitabine, standard induction chemotherapy of cytarabine and idarubicin, or supportive care only. Exclusion criteria included

patients who had prior cancer diagnoses and received other first line chemotherapeutic agents. YNHH provided a spreadsheet for every inpatient and outpatient visit with an AML diagnosis code. This spreadsheet included the following data: medical record number, encounter number, name, sex, race description, age, inpatient or outpatient encounter, admission date, discharge date, length of stay, principal ICD-9 code and description, secondary diagnoses by visit, and date of death (if at YNHH). The spreadsheet also indicated whether the following medications were used: 5-azacitidine, decitabine, cytarabine, doxorubicin, idarubicin, and gemtuzumab.

From the initial list of patient visits, 276 unique patients were identified (Figure 1). Of these patients, 58 patients were identified with primary AML diagnoses treated at YNHH. The other 218 patients were excluded for the following reasons: 49 patients were treated elsewhere and seen at YNHH in consultation or for laboratory purposes only; 21 patients had MDS but did not meet the criteria for AML; 62 patients had a prior history or primary diagnosis of another leukemia or lymphoma; 27 patients were either already in remission or had relapsed AML; 17 patients had a primary diagnosis of a solid tumor; 36 patients had no accessible medical record or no mention of AML in their record; and 6 patients had an initial AML diagnosis before age 65.

Of the 58 patients with primary AML diagnosis after age 65 treated at YNHH, 20 received decitabine therapy. Of those, 11 received decitabine alone as first-line

therapy while eight patients received it as second line treatment and one patient received decitabine and gemtuzumab ozogamicin in combination. The 38 remaining patients never received decitabine treatment. Of that group, 14 patients never received chemotherapeutic treatment. Eleven patients received standard induction therapy of cytarabine and idarubicin. Thirteen patients received other first-line treatments.

**Patient Cohorts**

Three patient groups were identified for further data analysis. These include 11 patients who received standard induction therapy of cytarabine and idarubicin, 11 patients who received decitabine alone as first line therapy, and 14 patients who received no chemotherapeutic treatment.

**Data Collection**

Collected raw data included date of diagnosis, date of death, number of cycles of chemotherapeutic treatment, number of days spent in the hospital, number of outpatient visits, cytogenetics and flow cytometry at time of diagnosis, complete blood count with differential at time of diagnosis, and use of other chemotherapeutic agents or hydroxyurea. Survival in months was calculated from date of diagnosis to date of death. When not available through the YNHH medical records, date of death was obtained via the United States Social Security Death Index at https://familysearch.org/.

**Data Analysis**

Statistics and graphs were generated using Microsoft Excel. P-values were calculated using a two-tailed, unpaired Student's *t*-test. P-values < 0.05 were considered significant. Confidence intervals were calculated using an α of 0.05. Kaplan-Meier curves were generated using XLSTAT-Life Survival Analysis Software (Addinsoft, Paris, France) based on [Gehan EA. A generalized Wilcoxon test for comparing arbitrarily singly-censored samples. Biometrika 1965;52:203-23].

**Author Contributions**

HIC approval was obtained by the author in collaboration with Dr. Peter Marks. Data collection and data analysis was done by the author under the mentorship of Dr. Peter Marks and Dr. Nikolai Podoltsev. Text and figures were completed by the author under the mentorship of Dr. Nikolai Podoltsev and Dr. Peter Marks.

## RESULTS

### Patient characteristics

Between January 2000 and December 2010, 58 patients age 65 or older had new diagnoses of AML (Figure 1). Of these patients, eleven received first-line treatment of idarubicin and cytarabine standard induction chemotherapy; eleven received first-line treatment with decitabine; and fourteen received supportive care.

Patient demographics and baseline clinical characteristics were not balanced among the three treatment groups (Table 1). The standard induction chemotherapy group was the youngest with a median age of 69 years (range, 65 to 76 years); this group was nearly evenly split with six patients in their sixties and five patients in their seventies. The decitabine group was statistically significantly older ($P$ = .020) with a median age of 77 years (range, 67 to 87 years); only three of the patients were in their sixties while seven patients were in their seventies and one patient was 87 years old. The supportive care group was the oldest and statistically significantly older ($P$ = .0005) than the decitabine group with a median age of 84.5 (range, 75 to 89 years). No patients receiving only supportive care were in their sixties and only three were in their seventies. The other eleven patients were all in their eighties.

There were more men in the standard chemotherapy (eight men, three women) and decitabine (seven men, four women) groups, but gender was evenly balanced in the no treatment group (seven men, seven women).

There were no statistically significant differences in complete blood counts upon initial diagnosis in the three treatment groups. The median white blood cell (WBC) count in all three groups was equal to or less than 5.0 x $10^9$/L. Median WBC counts at diagnosis were 4.8 x $10^9$/L (95% confidence interval (CI), -5.3 to 62.6 x $10^9$/L) in the standard chemotherapy group; 1.9 x $10^9$/L (95% CI, 1.5 to 11.9 x $10^9$/L) in the decitabine group, and 5.0 x $10^9$/L (95% CI, 0.7 to 56.1 x $10^9$/L) in the no treatment group. Three (27.3%) patients in the standard chemotherapy group, two (18.2%) patients in the decitabine group, and four (28.6%) patients in the supportive care group had initial WBC counts greater than 10 x $10^9$/L.

Initial median hemoglobin was nearly equivalent in the standard induction chemotherapy (9.3 g/dL; 95% CI, 8.1 to 10.7 g/dL) and decitabine (9.0 g/dL; 95% CI, 7.2 to 10.3 g/dL) groups but statistically insignificantly lower in the supportive care group at 7.5 g/dL (95% CI 6.5 to 8.3 g/dL). Median platelet counts upon initial diagnosis were 92,000/μL (95% CI, 59,000 to 125,000/μL) in the standard chemotherapy group, 46,000/μL (95% CI, 27,000 to 119,000/μL) in the decitabine group, and 66,000/μL (95% CI, 48,000 to 137,000/μL) in the supportive care group.

The standard induction chemotherapy group and decitabine group had similar cytogenetic profiles, as stratified by the Cancer and Leukemia Group B into favorable, intermediate, or adverse cytogenetic risk groups (22). The standard induction chemotherapy group had one patient with favorable cytogenetics, five patients with intermediate cytogenetics, and four patients with adverse

cytogenetics. One patient's cytogenetics is unavailable. The decitabine group had five patients with intermediate cytogenetics and five patients with adverse cytogenetics. Again, one patient's cytogenetics is unavailable. The supportive care group only had five patients with available cytogenetic information. Of those, three had intermediate and two had adverse cytogenetic risk.

**Treatment regimens**

All 11 patients in the standard induction chemotherapy group received a cytarabine and idarubicin 7 plus 3 regimen for remission induction of AML. On a 28 day cycle, this regimen calls for IV idarubicin on days 1, 2, and 3 and continuous IV infusion of cytarabine on days 1 through 7.

Three patients (27.3%) achieved complete remission and subsequently received cytarabine consolidation treatment (Table 2). Four patients (36.4%) were refractory to the initial cytarabine and idarubicin 7 + 3 regimen and received other chemotherapeutic agents. One received two courses of high-dose cytarabine (HIDAC) and achieved complete remission that was followed by cytarabine consolidation treatment. Another patient achieved remission after receiving the FLAG regimen of fludarabine, cytarabine, and granulocyte colony-stimulating factor (G-CSF). Two more patients received one cycle of gemtuzumab ozogamicin and never achieved remission. None of the patients who received standard induction chemotherapy ever received hydroxyurea.

The 11 patients in the decitabine group received a median five cycles of decitabine (95% CI, 3.7 to 8.0 cycles) given over the course of five days every four or five weeks. One patient died and was unable to complete the first cycle. All other patients received a minimum three cycles. The highest number of cycles received was thirteen.

No patients receiving decitabine ever achieved a documented remission. Five patients proceeded to other chemotherapeutic agents. Four received gemtuzumab ozogamicin and one received clofarabine. Five of the eleven patients in the decitabine group also received hydroxyurea. The patients in the supportive care group received no chemotherapeutic agents, but four patients received hydroxyurea. There were no documented remissions in the supportive care group.

**Efficacy**

The patients receiving standard induction chemotherapy of idarubicin and cytarabine had a median overall survival of 7 months (95% confidence interval (CI), 3.5 to 9.4 months) (Figure 2). There was a favorable but nonsignificant ($P$ = .192) trend toward increased median overall survival in patients receiving decitabine. Decitabine patients had a median overall survival of 9 months (95% CI, 6.2 to 12.1 months).

Patients receiving only supportive care had a median overall survival of 0.6 months (95% CI, 0.2 to 3.3 months). These patients had statistically significantly worse

survival than both the standard induction chemotherapy ($P$ = .010) and decitabine ($P$ = .0003) groups.

**Hospitalization**

There was a statistically significant ($P$ = .047) trend toward a decreased number of hospital days in patients receiving decitabine in comparison to those receiving standard induction chemotherapy. The standard induction chemotherapy group spent a median 41 days (95% CI, 32.6 to 99.4 days) in the hospital while the decitabine group spent a median 30 days (95% CI, 17.7 to 42.9 days) in the hospital (Figure 3).

When overall survival is taken into account, decitabine patients spent a significantly smaller proportion ($P$ = .047) of their lives in the hospital. To account for the increased survival in the decitabine group, the number of days each patient spent in the hospital was divided by the overall number of days the patient lived following their AML diagnosis. Patients undergoing standard induction chemotherapy spent a median 33.1% (95% CI, 28.7% to 67.9%) of their time admitted in the hospital while patients receiving decitabine spent a median 8.8% (95% CI, 4.6% to 35.5%) of their time in the hospital.

Patients receiving supportive care only spent a median 3.5 days (95% CI, 1.4 to 10.6 days) in the hospital. However, since their overall survival was reduced, these

patients still spent a median 25.0% (95% CI, 14.7% to 53.6%) of their days following diagnosis in the hospital.

**Outpatient visits**

Instead of spending more time in the hospital, patients receiving decitabine therapy had a statistically significant ($P$ = .036) increased number of outpatient visits when compared to those receiving standard induction chemotherapy. The standard induction chemotherapy group had a median 1 outpatient visit (95% CI, -0.7 to 11.8 visits) while the decitabine group had a median 12 outpatient visits (95% CI, 11.0 to 75.7 visits) (Figure 3).

Only four of the fourteen patients receiving supportive care only ever had a hematology/oncology outpatient visit for a median zero visits (95% CI, -0.13 to 1.28 visits).

Early Death

Early death is defined as patients who die within 30 days of diagnosis and is used as a surrogate for regimen-related toxicity (22). Two patients (18.2%) receiving standard induction chemotherapy and one patient (9.1%) receiving decitabine experienced early death. Eight patients (57.1%) receiving only supportive care died within 30 days of diagnosis.

Adverse events cannot be reported due to the retrospective nature of this study and the absence of comprehensive information available in the medical record.

## DISCUSSION

The median age of AML diagnosis is 66 years, yet older patients have significantly worse prognosis. They are more likely to have adverse forms of the disease, poor functional status, and poor tolerance for intensive chemotherapy. Patients who achieve complete remission through intensive chemotherapy are more likely to have increased survival and quality of life (4). However, older patients are less likely to receive intensive chemotherapy and those that do are more likely to experience early death and less likely to achieve remission (19,48). Low-intensity and alternative regimens have been trialed in older AML patients with mixed results (50). One in particular, the hypomethylating agent decitabine, has demonstrated complete remission rates ranging from 25 to 47%. More importantly, decitabine has demonstrated median survival in older AML patients that is comparable to other chemotherapeutic agents (70-72).

This single-center retrospective review of AML patients over age 65 sought to determine quality of life, measured by hospital days and outpatient visits, in three treatment groups: standard induction chemotherapy of idarubicin and cytarabine, decitabine therapy, and supportive care only.

### Baseline characteristics

The demographics and baseline characteristics of the three groups were not balanced. Those receiving standard induction chemotherapy were younger than those receiving decitabine who in turn were younger than those receiving only

supportive care. This is not surprising as standard induction chemotherapy is associated with significant toxicities and is often poorly tolerated by older patients (44). Decitabine was likely chosen for slightly older patients who still desired treatment but were either not candidates or unwilling to undergo the more toxic standard induction chemotherapy. The group opting for supportive care was significantly older than the two treatment groups, with a median age of 84.5 years. It is not surprising then that these patients were unwilling or unable to undergo any treatment.

The median WBC at diagnosis was nonsignficantly higher in the standard induction chemotherapy and supportive care groups than the decitabine group. This could be explained by the fact that elevated WBC is known to be a poor-risk feature in AML patients undergoing decitabine treatment (74). Therefore, it is likely some of the patients with higher WBC were poor candidates for decitabine therapy and therefore received either standard induction chemotherapy or supportive care.

Cytogenetic profiles of the standard induction chemotherapy and decitabine groups were nearly identical. The only patient with a favorable cytogenetic profile received standard induction chemotherapy, a logical decision as this patient was more likely to respond to the regimen and standard induction chemotherapy offers the greatest probability of complete remission and cure. Patients who opted for supportive care often never underwent cytogenetic work-up as the results were not going to change their treatment plans.

**Remission**

In patients receiving standard induction chemotherapy, determining whether a patient has achieved remission is critical for treatment decisions. Three patients (27.3%) in this study achieved complete remission following their initial course of standard induction chemotherapy. This is slightly lower than similar studies with complete remission rate of 42% to 52% (44,73). In this study, two additional patients achieved complete remission on other agents after being refractory to standard induction chemotherapy. This brought the total remission rate to 45.5%. None of the patients receiving decitabine therapy had a confirmed complete remission. In this group of older patients, achieving remission most likely would not have changed clinical decision-making and therefore the patients were spared unnecessary bone marrow biopsies. Other decitabine studies have demonstrated complete remission rates ranging from 15.7% to 28% (70,72,73). Current research is exploring using decitabine to achieve complete remission with the goal of proceeding to bone marrow stem cell transplant. Patients in this study received a median five cycles of decitabine compared with three cycles in another similar study (70).

**Overall survival**

Median overall survival in the standard induction chemotherapy group was 7 months, within a range of 6.7 to 12.8 months seen in other studies (44,73). Decitabine patients had median survival of 9 months, compared with a range of 7.7

to 8.8 months seen in other studies (70,72,73). Patients in this study receiving supportive care only had a poor median survival of 0.6 months, considerably less than the range of 1.7 to 5 months seen in other studies (48,72). This study demonstrated a nonsignificant but positive trend for increased survival in older patients receiving decitabine therapy when compared to standard induction chemotherapy. This finding is consistent with other papers demonstrating decitabine to be superior or not inferior in this older and difficult to treat patient group (70,72,73).

Achieving remission has long been the goal in AML patients, as remission was believed to lead to increased survival and improved quality of life (4). Yet this study and others demonstrate that increased survival is not contingent on achieving remission or even assessing whether remission has been achieved. Instead, other forms of leukemic response, such as to the hypomethylating agent decitabine, can be effective in reducing mortality in older patients with AML (44,70,72,73).

**Quality of life**

While overall survival had been assessed in prior studies comparing decitabine to other chemotherapeutic agents, quality of life has not been studied. Given the retrospective nature of this study, it was not possible to measure quality of life using traditional questionnaires (75). As a surrogate for quality of life, the number of days spent in the hospital and the number of outpatient visits were examined. While not a comprehensive assessment, this data does offer some insights into of quality of life

and was possible to gather posthumously. Patients receiving decitabine spent significantly fewer days in the hospital (30 versus 41 days) and a significantly smaller proportion of their lives (8.8% versus 33.1%) from diagnosis to death in the hospital. However, this does not mean the decitabine patients received less medical care. Instead, their care was shifted to the outpatient setting where they had significantly more visits (12 versus 1 visits) than those receiving standard induction chemotherapy.

Given the retrospective nature of this study and the variability in accessible medical records, it was not possible to give a full account of treatment related adverse events. Instead, early death, defined as mortality within 30 days of initiation of chemotherapy, is a standard for assessing chemotherapy toxicity (4,76). The early death rates for both standard induction chemotherapy and decitabine therapy were low, 18.2% and 9.1%, respectively. These numbers compare well to the Swedish Acute Leukemia Registry of more than 800 patients over age 65 receiving intensive chemotherapy in which 13.3% of patients experienced early death (4). A large number of early deaths were seen in the supportive care only group where 57.1% of patients died within 30 days. This is not surprising as the supportive care group was significantly older and likely had a very poor performance status that made them unfit to attempt therapy. The 57.1% in this study was greater than the 39% of nearly 1000 patients in the Swedish Acute Leukemia Registry receiving supportive care only who died within 30 days of diagnosis (4).

This study was limited in several ways. As a retrospective chart review, there was no randomization. Initial characteristics of the three patient groups were not matched, most importantly in terms of age. Some data, such as treatment-related adverse events and initial cytogenetics, was not accessible for all patients. Patients undergoing decitabine therapy did not have bone marrow biopsies, making it impossible to determine if they had achieved remission. The number of patients in this single-institution study was small, limiting the ability to achieve statistical significance in survival differences.

In conclusion, this retrospective study of first-line treatment of older patients with AML found fewer inpatient days and a positive trend for increased survival in patients receiving decitabine therapy compared to patients receiving standard induction chemotherapy. It is important to note that the decitabine group did better despite the fact that it was significantly older than the standard induction chemotherapy group and would therefore be expected to do worse. This study is novel in its inclusion of inpatient days as another metric by which decitabine is superior to standard induction chemotherapy.

It would potentially be helpful and empowering for patient decision-making if differences in quality of life for AML treatment regimens were made known. Patients who receive decitabine therapy can expect to require less hospital care but more outpatient visits in comparison to those receiving standard induction chemotherapy. Given the limited life expectancy and very high one-year mortality in

AML, providing patients with the most information possible regarding the options for how they spend their time would be beneficial.

## FIGURES AND TABLES

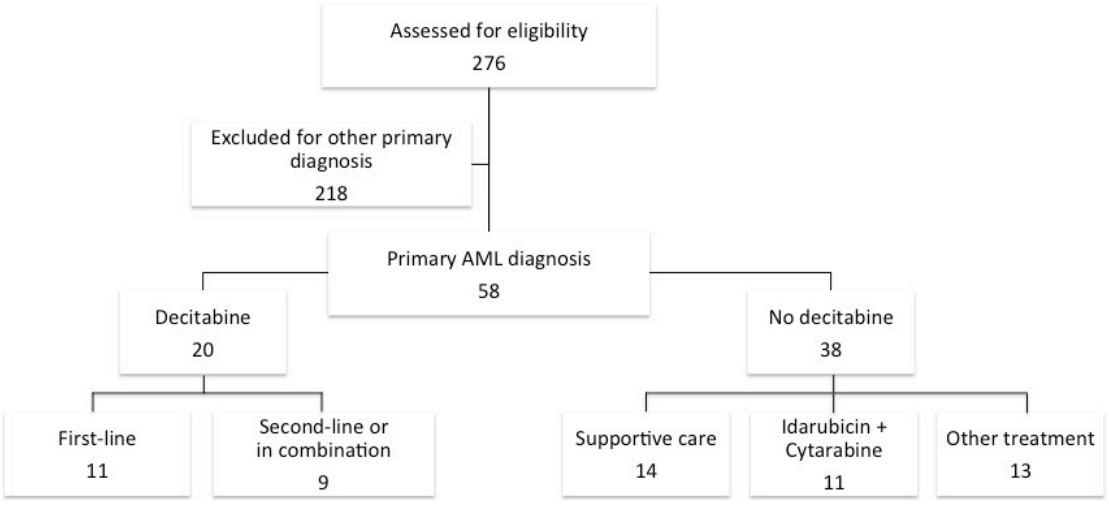


**Figure 1. Participant flow diagram.**

Demonstrates inclusion and exclusion criteria for 276 patients assessed for eligibility in this study. The three groups ultimately chosen for this study included 11 patients receiving first-line decitabine, 14 patients receiving supportive care only, and 11 patients receiving first-line idarubicin + cytarabine standard induction chemotherapy.

| | Standard Induction | | Decitabine | | Supportive Care | |
|---|---|---|---|---|---|---|
| | No. of Patients | % | No. of Patients | % | No. of Patients | % |
| Age, years | | | | | | |
| Median | 69 | | 77 | | 84.5 | |
| Range | 65-76 | | 67-87 | | 75-89 | |
| 65-69 | 6 | 54.5% | 3 | 27.3% | 0 | 0% |
| ≥ 70 | 5 | 45.5% | 8 | 72.7% | 14 | 100% |
| Sex | | | | | | |
| Male | 8 | 72.7% | 7 | 63.6% | 7 | 50% |
| Female | 3 | 27.3% | 4 | 36.4% | 7 | 50% |
| White blood cells, 10^9/L | | | | | | |
| Median | 4.8 | | 1.9 | | 5 | |
| Range | 1.6-175 | | 0.9-25.8 | | 0.9-149 | |
| Hemoglobin, g/dL | | | | | | |
| Median | 9.3 | | 9 | | 7.45 | |
| Range | 6-12.9 | | 4-12.6 | | 4.9-10.1 | |
| Platelets, /µL | | | | | | |
| Median | 92,000 | | 46,000 | | 66,000 | |
| Range | 27,000-185,000 | | 15,000-235,000 | | 10,000-280,000 | |
| Cytogenetics | | | | | | |
| Favorable | 1 | 9.1% | 0 | 0.0% | 0 | 0.0% |
| Intermediate | 5 | 45.5% | 5 | 45.5% | 3 | 21.4% |
| Adverse | 4 | 36.4% | 5 | 45.5% | 2 | 14.3% |
| Unavailable | 1 | 9.1% | 1 | 9.1% | 9 | 64.3% |

**Table 1. Patient demographics and baseline clinical characteristics.**

There exist statistically significant differences in age between standard induction chemotherapy and decitabine groups ($P$ = .020) and between decitabine and supportive care groups ($P$ = .0005). There were no statistically significant differences in sex, white blood cells, hemoglobin, platelets, or cytogenetics.

| Sex | Age | Cytogenetic Risk | Cycles | Remission after initial agent | Agents after initial induction | Remission with other agents | Survival, months | Inpatient days | % of days in hospital | Outpatient days |
|---|---|---|---|---|---|---|---|---|---|---|
| **Standard Induction Chemotherapy** | | | | | | | | | | |
| M | 69 | Adverse | 2 | No | None | N/A | 7.0 | 32 | 15.2% | 5 |
| M | 72 | Intermediate | 3 | No | FLAG | Yes | 15.0 | 99 | 22.0% | 15 |
| M | 76 | Intermediate | 1 | No | None | N/A | 0.5 | 15 | 100.0% | 1 |
| M | 69 | Favorable | 2 | No | HIDAC, Consoldation | Yes | 8.0 | 177 | 73.8% | 1 |
| F | 74 | Intermediate | 1 | No | Gemtuzumab | No | 7.0 | 41 | 19.5% | 2 |
| M | 65 | Adverse | 1 | No | None | N/A | 4.0 | 24 | 20.0% | 1 |
| M | 65 | Intermediate | 1 | Yes | Consolidation | N/A | 6.0 | 35 | 19.4% | 1 |
| F | 71 | Intermediate | 1 | Yes | Consolidation | N/A | 13.0 | 129 | 33.1% | 27 |
| F | 68 | Not available | 2 | No | Gemtuzumab | No | 1.5 | 50 | 98.0% | 1 |
| M | 69 | Adverse | 1 | No | None | N/A | 1.0 | 27 | 90.0% | 1 |
| M | 71 | Adverse | 2 | Yes | Consolidation | N/A | 8.0 | 97 | 40.4% | 14 |
| **Median** | 69 | | 1 | | | | 7.0 | 41 | 33.1% | 1 |
| **Stdev** | 3.232 | | 0.66 | | | | 4.44 | 49.75 | 33.1% | 8.27 |
| **Decitabine** | | | | | | | | | | |
| M | 74 | Adverse | 13 | No | Gemtuzumab | No | 17.0 | 45 | 8.8% | 115 |
| M | 87 | Not available | 8 | No | None | N/A | 9.0 | 2 | 0.7% | 93 |
| M | 78 | Intermediate | 1 | No | Hydroxyurea | No | 0.5 | 15 | 93.8% | 1 |
| F | 68 | Adverse | 5 | No | Clofarabine | No | 7.0 | 9 | 4.3% | 12 |
| M | 73 | Intermediate | 3 | No | Gemtuzumab, Hydroxyurea | No | 4.0 | 56 | 46.7% | 5 |
| M | 77 | Adverse | 5 | No | Gemtuzumab, Hydroxyurea | No | 7.0 | 35 | 16.7% | 9 |
| M | 78 | Intermediate | 5 | No | None | N/A | 12.0 | 30 | 8.3% | 6 |
| F | 79 | Adverse | 4 | No | None | N/A | 9.0 | 12 | 4.4% | 16 |
| F | 67 | Intermediate | 5 | No | Hydroxyurea | No | 10.0 | 55 | 18.3% | 6 |
| F | 77 | Intermediate | 10 | No | Gemtuzumab | No | 15.0 | 52 | 11.6% | 127 |
| M | 69 | Adverse | 5 | No | Hydroxyurea | No | 10.0 | 22 | 7.3% | 87 |
| **Median** | 77 | | 5 | | | | 9.0 | 30 | 8.8% | 12 |
| **Stdev** | 5.557 | | 3.19 | | | | 4.43 | 18.76 | 26.1% | 48.12 |
| **P-value** | 0.017 | | | | | | 0.192 | 0.046 | 0.047 | 0.026 |
| **No treatment** | | | | | | | | | | |
| M | 82 | Not available | | No | None | N/A | 0.3 | 6 | 66.7% | 0 |
| F | 89 | Not available | | No | None | N/A | 2.0 | 2 | 3.3% | 0 |
| F | 85 | Intermediate | | No | Hydroxyurea | No | 0.3 | 6 | 85.7% | 0 |
| F | 85 | Not available | | No | None | N/A | 4.0 | 28 | 23.3% | 3 |
| M | 89 | Not available | | No | Hydroxyurea | No | 3.0 | 3 | 3.3% | 3 |
| M | 86 | Not available | | No | Hydroxyurea | No | 0.3 | 8 | 100.0% | 0 |
| M | 85 | Not available | | No | None | N/A | 0.1 | 2 | 66.7% | 0 |
| F | 78 | Adverse | | No | None | N/A | 0.5 | 4 | 26.7% | 1 |
| M | 84 | Intermediate | | No | Hydroxyurea | No | 0.1 | 1 | 33.3% | 0 |
| F | 84 | Not available | | No | None | N/A | 9.0 | 7 | 2.6% | 0 |
| F | 75 | Adverse | | No | None | N/A | 2.0 | 2 | 3.3% | 1 |
| M | 89 | Not available | | No | None | N/A | 0.8 | 12 | 53.3% | 0 |
| F | 77 | Intermediate | | No | None | N/A | 0.5 | 1 | 6.7% | 0 |
| M | 81 | Not available | | No | None | N/A | 2.0 | 2 | 3.3% | 0 |
| **Median** | 84.5 | | | | | | 0.63 | 3.50 | 25.0% | 0.00 |
| **Stdev** | 4.289 | | | | | | 2.32 | 6.82 | 33.0% | 1.05 |

**Table 2. Treatment Response.**

Select demographics, baseline characteristics, and treatment response for each patient in this study. Median values and standard deviations are presented for age, survival, inpatient days, percentage of life from diagnosis to death spent in the hospital, and outpatient days. *P*-values compare the standard induction chemotherapy and decitabine groups; the supportive care group was not included in the above *P*-value calculations. Statistically significant differences were observed in patient age, number of days spent in the hospital, percentage of time spent in the hospital, and outpatient days.

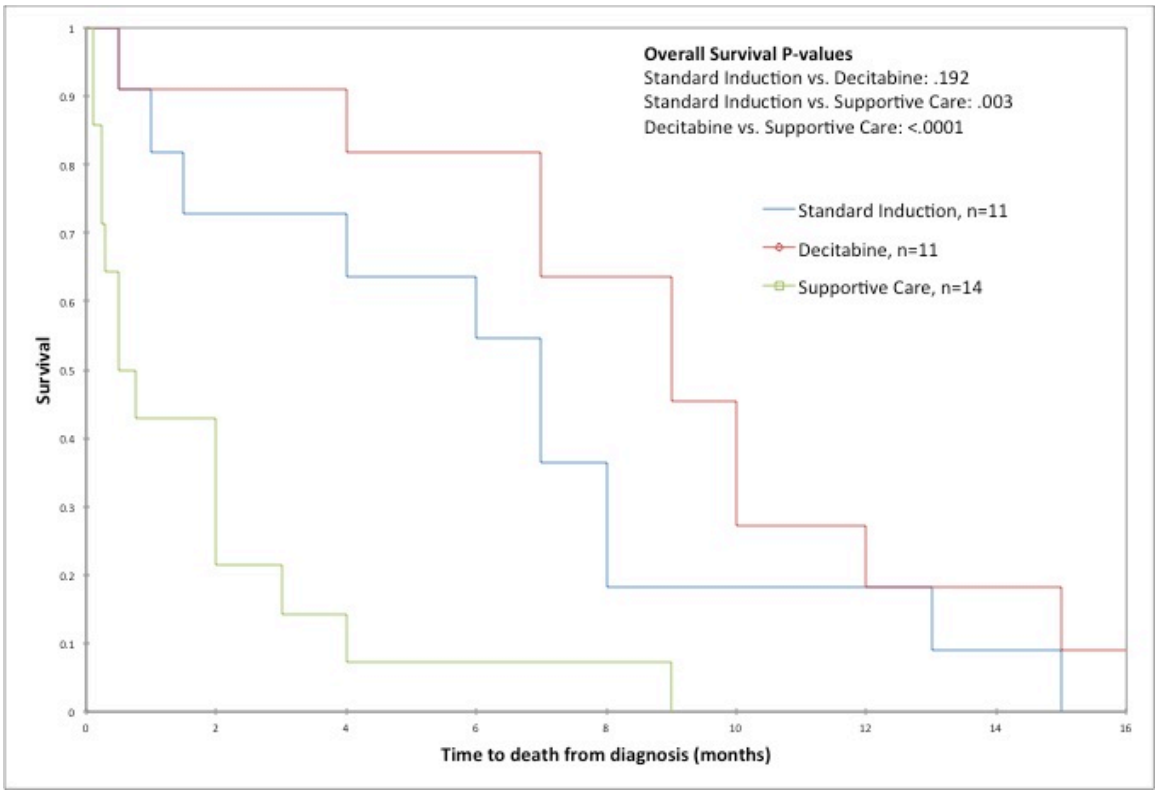


**Figure 2. Overall Survival.**

Kaplan-Meier curve of overall survival in the three treatment groups. There was no statistically significant difference in overall survival between the standard induction chemotherapy and decitabine groups but the supportive care only group had significantly worse survival than the other two groups.

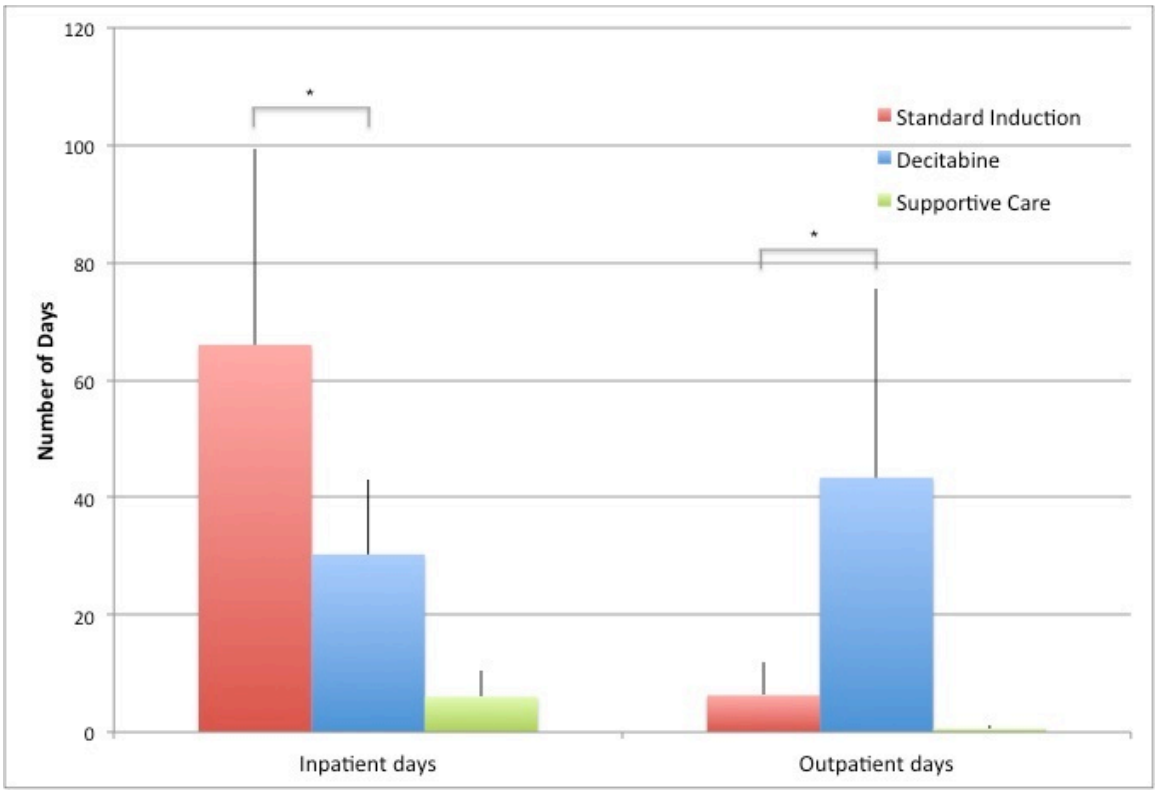


**Figure 3. Inpatient and Outpatient Days.**

Mean number of days spent in the hospital as an inpatient and mean number of outpatient visits. Error bars demonstrate 95% confidence interval. There were statistically significant differences (* $P < .05$) between the standard induction chemotherapy and decitabine groups in both inpatient and outpatient days. Statistical significance was not calculated for the supportive care group.

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