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

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See related Editorial on pages 1007–10, this issue.

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BACKGROUND. The survival of older patients with acute myeloid leukemia has not improved. Few clinical trials have been available for older patients who are not considered fit for an intensive chemotherapy approach.

METHODS. Between December 1998 and November 2003, as part of National Cancer Research Institute Acute Myeloid Leukemia 14 Trial, 217 patients, who were deemed unfit for intensive chemotherapy were randomized to receive low-dose cytarabine (Ara-C) (20 mg twice daily for 10 days) or hydroxyurea with or without all-trans retinoic acid (ATRA).

RESULTS. Low-dose ara-C produced a better remission rate (18% vs 1%; odds ratio [OR], 0.15; 95% confidence interval [95% CI], 0.06–0.37; $P = .00006$) and better overall survival (OR, 0.60; 95% CI, 0.44–0.81; $P = .0009$), which was accounted for by the achievement of complete remission (CR) (duration of CR: 80 weeks vs 10 weeks for patients with no CR). Patients who had adverse cytogenetics did not benefit. ATRA had no effect. Toxicity scores or supportive care requirements did not differ between the treatment arms.

CONCLUSIONS. Older, less fit patients have a poor outcome, and few trials have been conducted in this patient group. Low-dose ara-C treatment was superior to best supportive care and hydroxyurea because it had greater success in achieving CR, and it could represent standard care against which new treatments may be compared in this patient group. [See editorial on pages 1007–10, this issue.]
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KEYWORDS: acute myeloid leukemia, all-trans retinoic acid, complete remission, hydroxyurea, low-dose cytarabine, myelodysplastic syndrome, toxicity.

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The median age of patients with acute myeloid leukemia (AML) is 65 years. Results from several collaborative group studies have confirmed that the prognosis for older patients (>60 years) is unsatisfactory (<20% at 5 years; median survival, 9–12 months). Furthermore, those studies suggest that, unlike the experience in younger patients, there has been little improvement in survival in the last 2 decades. Such trials usually have offered an intensive treatment approach, and it is by no means clear that the patients recruited are representative of AML in older patients. Thus, there is a substantial group of older patients who are not entered into the clinical trials on offer, as corroborated in the Surveillance, Epidemiology, and End Results data, which indicate that only 30% of older patients with AML receive intensive chemotherapy.[1] Among the several possible reasons for their omission from trials is that older patients are not considered fit for an intensive treatment approach. Instead, they will receive a treatment approach that truly is palliative and is aimed at optimizing quality rather than quantity of life. Very few randomized trials have been undertaken in this patient group, with the result that there is no established treatment approach. The number of patients with AML who require treatment will increase as the general population in this age group increases, and new chemotherapy agents are being developed that may be useful for this group of patients.

In its 34-year history of clinical trials, the United Kingdom Medical Research Council Leukaemia Working Party has never devised a clinical trial for older patients that offered any course other than an intensive treatment approach; thus, trials were applicable only to the selected group of patients who were considered fit. The question of which patients would benefit from being treated intensively or nonintensively remains important. Two previous studies randomized patients between intensive and nonintensive treatments.[2,3] Although the responses were significantly better in intensively treated patients, there was no significant difference in survival. This reflects the dilemma, that, although greater intensity may result in a higher remission rate, it is associated with more nonleukemic deaths and, thus, no survival advantage. In the United Kingdom National Cancer Research Institute AML14 Trial, where there was uncertainty, investigators could randomize patients between an intensive approach and a nonintensive approach; and, within each approach, additional randomizations were available. Among 1400 recruited patients, only 8 patients were randomized between the 2 approaches, suggesting that, for whatever reason, either patients or their physicians were clear about which approach to adopt. Here, we report the results of the randomized comparisons that were undertaken in the nonintensive approach.

Low-dose (LD) cytarabine (Ara-C) has been used in various schedules for several years, with several Phase II trials in AML and myelodysplastic syndrome (MDS) showing responses that included complete remission (CR) of disease.[4–11] It is well tolerated and can be given in the outpatient or home care setting. Its mechanism of action at low doses is not completely clear: Some believe that it retains cytotoxic action, and some have view that it induces apoptosis by differentiation induction.[12,13] There is also a perception that LD ara-C induces excess cytopenia,

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thereby defeating the objectively of being optimally tolerable to the older patient. An alternative and widely used approach is to provide best supportive care, which includes blood product support and antibiotic treatment, as required with periodic treatment with hydroxyurea (HU) to control the peripheral white blood count.

All-trans retinoic acid (ATRA) treatment has revolutionized the treatment of acute promyelocytic leukemia (APL), in which the presence of the promyelocytic leukemia (PML)-retinoic acid receptor α fusion protein denotes sensitivity. Various in vitro data have suggested that primary leukemic blast cells also can be induced to differentiate.[14,15] This is supported by anecdotal reports of patients with AML and MDS showing a response to retinoid treatment as a single agent. Of potential interest is the preclinical data indicating that retinoid can sensitize leukemic blasts to ara-C, possibly by shortening the half-life of BCL-2, thus increasing the apoptotic stress.[16–20] Because the overexpression of BCL-2 has been suggested as a reason for resistance to treatment, there is a rationale for combining ATRA with chemotherapy in non-APL cases.[21]

Based on these issues and some nonrandomized Phase II data,[22] we designed a prospective randomized trial, Leukaemia Research Fund AML14, which offered initial randomization to an intensive approach or a nonintensive approach, and provided further randomizations of both approaches. Here, we report the nonintensive component of the trial. The objective was to compare LD ara-C with HU, both with supportive care, with respect to efficacy, toxicity, and supportive care requirements. In addition, patients would be randomized to receive or not to receive ATRA.

MATERIALS AND METHODS

In total, 1485 patients entered the trial, of whom only 8 patients were randomized between the intensive approach and the nonintensive approach. Two hundred twelve patients were not considered fit by the local investigator for the intensive treatment options and were randomized to receive the nonintensive approach. No specific criteria for defining such patients were used, except that patients aged <70 years should have a documented comorbidity that precluded chemotherapy. Patients were primarily aged >60 years, although younger patients could be entered. Any type of AML (de novo or secondary) and high-risk MDS (defined as $>10\%$ bone marrow blasts) were eligible. APL and blast transformation of chronic myeloid leukemia were excluded. The protocol was reviewed by the Clinical Trial Advisory Panel of the Leukaemia Research Fund and was approved by the Wales Multicentre Ethics Committee as well as each institution's ethical committee. The characteristics of all 1485 patients are shown in Table 1, split by initial treatment type (intensive vs nonintensive). Patients who entered the nonintensive approach were significantly older, had a poorer performance score, had more secondary disease, and had more heart disease and documented comorbid conditions. The results of the intensive treatment randomizations will be reported elsewhere.

Treatment

On entry, patients were allocated randomly to receive LD ara-C 20mg twice daily by subcutaneous injection for 10 days or HU sufficient to keep the white blood cell count below 10×10^9/L. Subsequent courses of LD-Ara-C were administered after intervals of 4 to 6 weeks. Patients also were randomized to receive ATRA 45 mg/m^2 per day for 60 days. Policies with regard to blood product support, antibiotic and antifungal prophylaxis, and treatment of febrile neutropenia were determined by established local practice.

Assessment of Response

CR

CR was defined by bone marrow aspiration, which was required to consist of $>50\%$ normal cellularity with evidence of trilineage maturation and $<5\%$ bone marrow blasts, no evidence of extramedullary disease, and regeneration of the peripheral neutrophil count to 1.0×10^9/L and the platelet count to 100×10^9/L. The persistence of myelodysplastic features did not exclude the diagnosis of CR.

Toxicity criteria

The maximum toxicities were recorded and graded according version 2 of the National Cancer Institute Common Toxicity Criteria.

Definitions of response endpoints

The following definitions also were used: overall survival (OS) is the time from randomization to death from any cause; for remitters, disease-free survival (DFS) is the time from CR to first event (either recurrence or death in CR).

Statistical Methods

Randomization was performed by telephone call to the central trial office. Allocation was computer generated using minimization to ensure balance overall and within stratification parameters: age groups (ages <60 years, 60–64 years, 65–69 years, 70–74 years, and ≥ 75 years), World Health Organization

TABLE 1
Characteristics of Patients Entering National Cancer Research Institute Acute Myeloid Leukemia Trial 14

Characteristic	No. of patients (%)		
	Intensive chemotherapy	Nonintensive chemotherapy	*P*
No. of randomized patients	1273	212	
Age group, y			
<60	33 (3)	4 (2)	<.0001
60–64	370 (29)	15 (7)	
65–69	505 (40)	28 (13)	
70–74	263 (21)	62 (29)	
≥75	102 (8)	103 (49)	
Sex			
Women	501 (39)	95 (45)	.03
Men	772 (61)	117 (55)	
Type of disease			
De novo AML	920 (72)	126 (59)	.003
Secondary AML	211 (17)	57 (27)	
MDS	142 (11)	29 (14)	
WBC, $\times 10^9$/L			
<100	1135 (89)	191 (90)	.8
100–199	104 (8)	15 (7)	
≥200	34 (3)	6 (3)	
Performance status			
0	721 (57)	55 (26)	<.0001
1	427 (34)	93 (44)	
2	75 (6)	36 (17)	
3	39 (3)	26 (12)	
4	11 (1)	2 (1)	
Heart disease*	206 (17)	54 (27)	.0006
Any other comorbidity*	404 (33)	98 (49)	<.0001
Thyroid dysfunction	28	7	.3
Hypertension	109	32	.002
Asthma	27	7	.3
Arthritis	33	9	.17
Diabetes	78	10	.4
Renal disease	16	5	.2
Concurrent cancer	26	9	.05
Respiratory disease	20	7	.07

AML indicates acute myeloid leukemia; MDS, myelodysplastic syndrome; WBC, white blood cells.
* Based on a total of 1420 patients with data available (1220 vs 200). Comorbidities are those experienced by ≥20 patients.

(WHO) performance status, white blood count (<100 × 10^9/L, 100–199 × 10^9/L, ≥200 × 10^9/L), and type of disease (de novo AML, secondary AML, MDS).

The primary endpoint was survival from randomization. The trial sample size was calculated on the basis that, to detect a 10% improvement in survival from 10% to 20% at 2 years, at a 2-tailed *P* value of .05. with 90% power, would require 200 patients per arm. The trial was closed by the Trial Steering Committee in November 2003 after a recommendation from the independent Data Monitoring and Ethics Committee.

For time to event endpoints, Kaplan-Meier life tables were constructed and were compared by using the log-rank test. Surviving patients were censored at April 1, 2005, when follow-up was up to date for 99% of patients (the 2 patients who were lost to follow-up were censored at the date they were last known to be alive).

Categorical endpoints (eg, CR rates) were compared between arms by Fisher exact tests. Continuous variables (eg, blood counts and supportive care requirements) were analyzed by parametric tests (*t* tests) or nonparametric tests (Wilcoxon) as appropriate.

Interactions between the 2 randomized comparisons were investigated by stratified analyses, ie, with each comparison adjusted for the other, using tests for heterogeneity over strata. In addition to the overall analyses of the randomized comparisons, subgroup analyses were performed by using the predefined stratification parameters (see above); although, because of the small numbers, some groups were combined to give larger numbers and greater statistical reliability (eg, performance status scores of 2, 3, and 4 were grouped together). Tests for heterogeneity of and/or trend in treatment effect between subgroups were performed. Because of the well-known dangers of subgroup analysis, all such analyses are interpreted cautiously.

Odds ratios (ORs) or hazard ratios (HRs) with 95% confidence intervals (95% CIs) were calculated for the main endpoints (CR and OS). For all endpoints, an OR/HR <1 indicated a benefit for LD ara-C over HU or for ATRA over no ATRA. All *P* values are 2 tailed. All analyses were performed on the *intention to treat* principle, with all patients analyzed in their allocated arms, irrespective of whether or not they actually received their allocated treatment.

RESULTS

Between December 1998 and November 2003, 1485 patients were entered into the trial overall; of these, 217 patients were entered into the nonintensive randomizations by 112 clinicians in 75 centers, including 129 patients with de novo AML, 58 patients with secondary AML, and 30 patients with high-risk MDS. The demographics of all patients recruited are provided in Table 1, which shows significant differences in the characteristics of patients entering the intensive and nonintensive approaches. The outcome of the intensive randomizations will be reported elsewhere. Among the patients who entered the nonintensive randomizations, the median age was 74 years (range, 51–90 years), with 4 patients aged <60 years and 165 patients aged >70 years. Two hundred two

TABLE 2
Patient Characteristics in the Nonintensive Randomizations

	HU versus Ara-C		ATRA	
Characteristic	**HU**	**Ara-C**	**ATRA**	**No ATRA**
No. of randomized patients	99	103	107	100
Age group, y				
<60	3	1	2	2
60–64	7	8	10	9
65–69	12	13	14	13
70–74	29	32	31	28
≥75	48	49	50	48
Sex				
Women	45	46	46	46
Men	54	57	61	54
Type of disease				
De novo AML	60	61	63	59
Secondary AML	25	28	27	28
MDS	14	14	17	13
WBC, $\times 10^9$/L				
<100	90	92	98	90
100–199	7	8	8	5
≥200	2	3	1	5
Performance status				
0	26	28	29	27
1	44	43	49	44
2	16	19	17	15
3	12	12	11	13
4	1	1	1	1
Cytogenetics*				
Favorable	1	2	3	0
Intermediate	52	54	58	54
Adverse	24	17	24	20
Unknown	22	30	22	26

HU indicates hydroxyurea; Ara-C, cytarabine; ATRA, all-trans retinoic acid; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; WBC, white blood cells.

*Risk was defined according to the criteria of Grimwade et al., 1999.[23]

patients were randomized between HU and LD ara-C, and 207 patients were randomized between ATRA and no ATRA. The baseline characteristics of the patients were balanced well between the arms (Table 2).

Treatment Compliance

Of the patients who were allocated to receive LD ara-C for whom data were available, 91% of patients received at ≥1 dose: 36% received 1 course; 15% received 2 courses; 9% received 3 courses; and 31% received ≥4 courses. Of the 105 patients who were randomized to receive ATRA, 90 received it for at ≥1 course.

Toxicity

The comparative toxicity is shown in Table 3. There were no significant differences between the LD-Ara-C and HU arms or between the ATRA and no ATRA arms. The toxicities observed in the first 8 weeks are shown in Table 4.

Supportive Care

There were no substantial differences between any of the treatment arms with respect to blood product support, hospitalization, days on antibiotics, or day case attendances to hospital (Table 5). There was a small but significantly greater requirement for day care visits for patients who received the second LD ara-C course.

Disease Response

Overall outcome

The overall CR rate was 9% (19 of 217 patients). Survival of the entire nonintensive population was 13% at 1 year, 4% at 2 years, and <1% at 3 years.

TABLE 3
Comparative Toxicity in Courses 1 and 2

	Course 1					Course 2				
	Mean grade		% grade 3/4			Mean grade		% grade 3/4		
Type of toxicity	**HU**	**Ara-C**	**HU**	**Ara-C**	***P****	**HU**	**Ara-C**	**HU**	**Ara-C**	***P****
Nausea/emesis	0.6	0.6	6	6	.8	0.4	0.4	2	2	.4
Alopecia	0.2	0.4	2	3	.08	0.1	0.5	3	5	.02
Oral	0.5	0.4	3	2	.18	0.4	0.5	0	6	.9
Diarrhea	0.5	0.5	10	4	.7	0.4	0.3	10	2	.9
Cardiac	0.5	0.5	11	10	.8	0.3	0.3	5	4	.7
	ATRA	**No ATRA**	**ATRA**	**No ATRA**		**ATRA**	**No ATRA**	**ATRA**	**No ATRA**	
Nausea/emesis	0.7	0.4	8	3	.07	0.4	0.3	2	0	.6
Alopecia	0.4	0.2	5	2	.16	0.4	0.3	5	3	.6
Oral	0.6	0.4	3	3	.09	0.5	0.4	3	2	.3
Diarrhea	0.6	0.4	6	7	.05	0.4	0.4	6	6	.7
Cardiac	0.5	0.5	13	9	.8	0.4	0.2	10	2	.3

HU indicates hydroxyurea; Ara-C, cytarabine; ATRA, *all*-trans retinoic acid.

* Wilcoxon test.

TABLE 4
Eight-Week Toxicity and Survival

Toxicity	Ara-C, n = 40	HU, n = 38
Infection	18	8
Hemorrhage	2	1
Stroke	1	0
Cardiac	0	1
Renal	2	1
Other	3	3
Resistant/progressive disease	14	14
Survival at 8 wks, %	61	62

Ara-C indicates cytarabine; HU, hydroxyurea.

TABLE 5
Supportive Care

	Mean		
Resource	HU	Ara-C	*P**
No. of blood units			
1	7	7	.8
2	5	6	.6
No. of platelet units			
1	7	9	.15
2	7	5	.6
No. of days on antibiotics			
1	7	7	.4
2	3	6	.8
No. of nights in hospital			
1	14	13	.3
2	8	6	.9
No. of day visits to hospital			
1	3	3	.7
2	3	5	.003
	ATRA	No ATRA	
No. of blood units			
1	7	7	.6
2	5	6	.9
No. of platelet units			
1	9	6	.09
2	6	5	.9
No. of days on antibiotics			
1	7	7	.5
2	2	7	.2
No. of nights in hospital			
1	13	13	.7
2	6	9	.8
No. of day visits to hospital			
1	3	3	.4
2	4	4	.9

HU indicates hydroxyurea; Ara-C, cytarabine; ATRA, *all*-trans retinoic acid.
* Wilcoxon rank-sum test.

CR

The CR rate was much better with LD ara-C than with HU (18% vs 1%, respectively; OR, 0.15; 95% CI, 0.06–0.37; $P < .00006$) (Table 6). In the LD ara-C arm, the mean time to CR for those who achieved it was 114 days (range, 50–313 days) for 6% of patients at the end of Course 1, for 33% of patients after Course 2, for 44% of patients after Course 3, and for 17% of patients after Course 4. The median disease-free survival for patients who achieved CR in the LD ara-C arm was 8 months. Fifteen patients developed recurrent disease, of whom 14 died later, including 2 patients who died in CR (of cerebrovascular accident and cardiac failure), and 1 patient remained in CR at 51 months after remission. In the ATRA comparison, the CR rates were 12% with ATRA and 8% with no ATRA (OR, 0.64; 95% CI, 0.26–1.58; $P = .3$).

OS

Survival with LD ara-C was better than with HU (OR, 0.60; 95% CI, 0.44–0.81; $P = .0009$) (Fig. 1). ATRA therapy did not improve survival overall or within either treatment arm (OR, 0.94; 95% CI, 0.71–1.23; $P = .6$) (Fig. 2). There was no significant evidence of interaction between HU/LD ara-C and ATRA (test for heterogeneity; $P = .07$) (Fig. 2).

In the LD ara-C arm, the achievement of CR was related strongly to survival, with a median survival of 66 days in nonremitters compared with 575 days in remitters (Fig. 3) (although, because remitters have to live long enough to achieve CR, this comparison does inflate the difference).

Subgroup analysis

There was no clear evidence that the beneficial effect of LD ara-C, compared was HU, was restricted to any particular type of patient (Fig. 4), although no remissions were observed in patients with adverse cytogenetics, which had an impact on the OS of the adverse-risk and intermediate-risk groups (Fig. 5). Similar treatment effects were observed for all ages, levels of white blood cells, and disease types. The number of patients with a poor performance status (WHO grades 3 and 4) was small, but there was some evidence that they did not benefit (test for trend; $P = .009$). However, there was a correlation between patients who had adverse cytogenetics and a poor performance score—the great majority of these patients died early (mean survival, 11 days). Older patients (aged >75 years) derived benefit from LD ara-C similar to that of younger patients (Fig. 6).

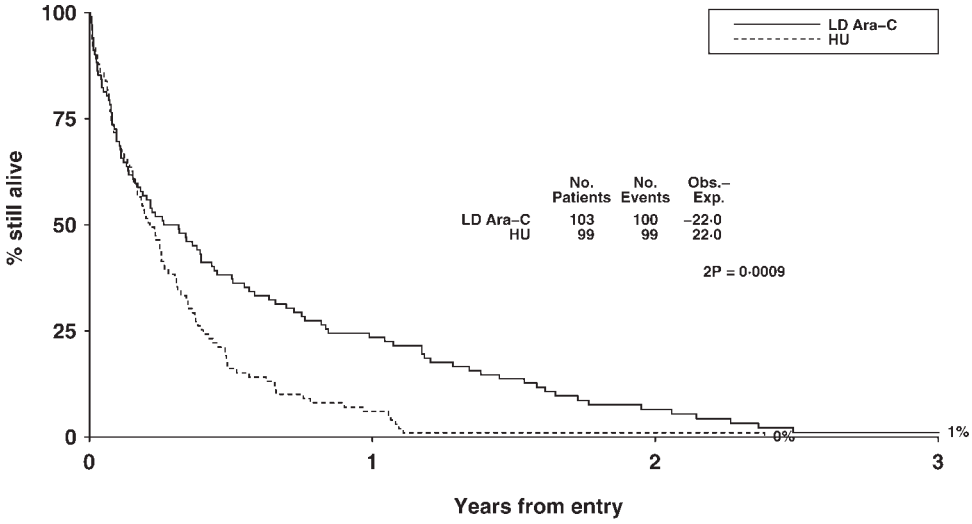
DISCUSSION

The treatment outcome for all older patients with AML is unsatisfactory and has not improved significantly over the last 2 decades in spite of improved

TABLE 6
Response

Variable	Ara-C, %	HU, %	OR (95% CI)*	*P*	ATRA, %	No ATRA, %	OR (95% CI)*	*P*
No. of patients with data available	102	99			107	99		
Response								
Induction death	26	26	1.01 (0.54–1.89)	1.0	28	22	1.36 (0.73–2.55)	.3
Resistant disease	56	73	0.48 (0.27–0.86)	.01	60	70	0.66 (0.26–1.58)	.14
CR	18	1	0.15 (0.06–0.37)	.00006	12	8	0.64 (0.26–1.58)	.3

Ara-C indicates cytarabine; HU, hydroxyurea; OR, odds ratio; 95% CI, 95% confidence interval; ATRA, *all*-trans retinoic acid; CR, complete remission.
* ORs ≥1 indicate better for HU and better for no ATRA. Induction death is defined as death from any cause within 30 days of randomization.



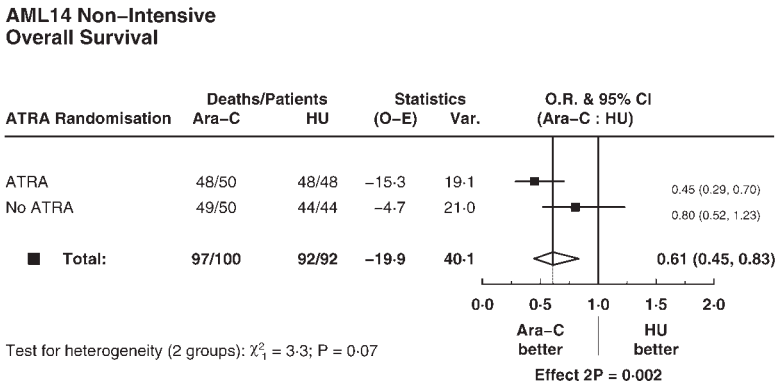
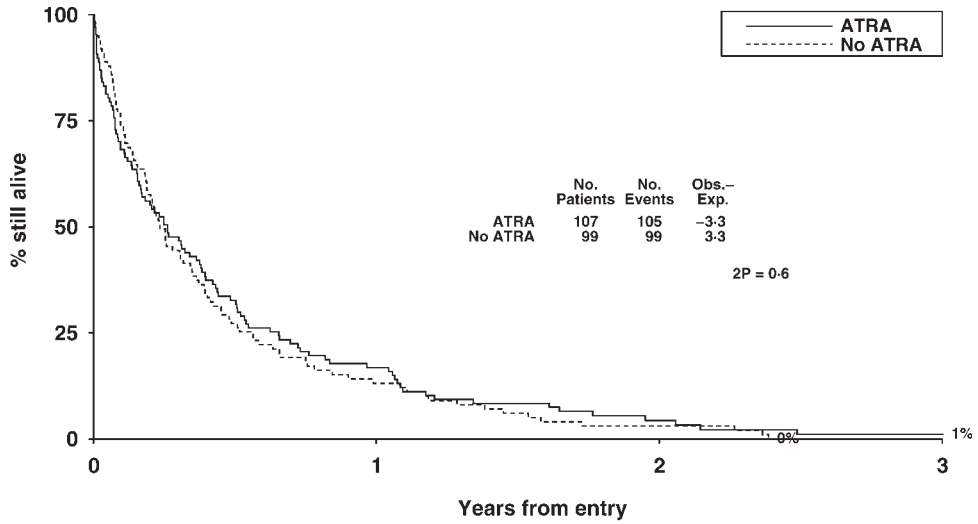


FIGURE 1. Overall survival: low-dose cytarabine (LD ara-C) versus hydroxyurea (HU). Obs. indicates observed; Exp., expected; AML14, National Cancer Research Institute Acute Myeloid Leukemia Trial 14; ATRA, all-trans retinoic acid; O-E: observed-expected; Var., variation; O.R., odds ratio; 95% CI, 95% confidence interval; 2P, 2-sided.

supportive care. Most treatment offered in the context of collaborative group clinical trials is intensive chemotherapy, but there is a substantial group of older patients that does not enter such trials either because they decline or because they are not considered fit enough. They are a neglected group; and, as the population demographics change, there will be a greater number of such patients. With this in mind, our study group conducted 1 of few randomized studies in this subgroup of patients.

LD ara-C was investigated extensively >20 years ago and is a familiar and practical schedule for older patients. Virtually all studies were nonrandomized and involved small patient numbers. The response to ara-C is dose dependent over a large dose range, and several LD schedules have been used, all of which can show at least some activity. It has never been demonstrated definitively that LD ara-C has its effect in patients because of the induction of differentiation or because of cytotoxicity, although the protracted



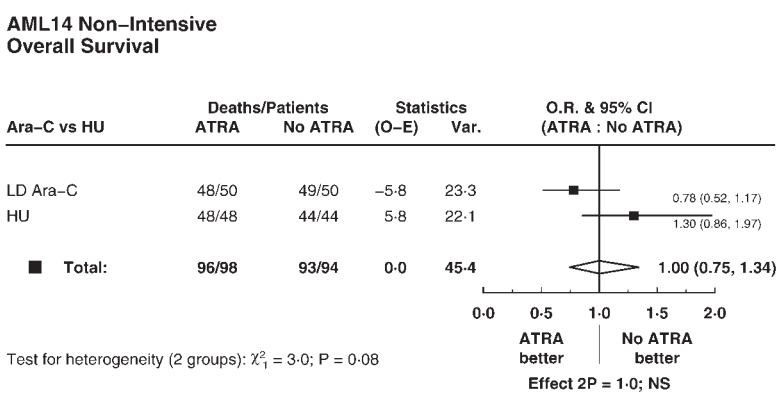


FIGURE 2. Overall survival: all-trans retinoic acid (ATRA) versus no ATRA. NS indicates nonsignificant; 2P, 2-sided.

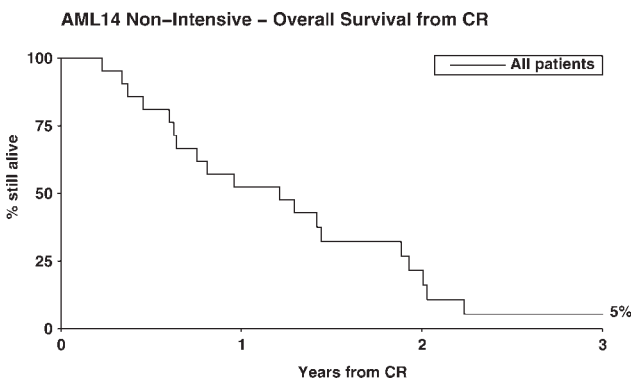


FIGURE 3. Survival after complete remission (CR).

time taken to respond and the preclinical data may support a differentiation mechanism. Conversely, in some studies, usually with the higher dose or longer duration schedules, a period of hypoplasia seemed to be associated with a greater prospect of response. There is no established LD schedule, and our selection of 20 mg twice daily for 10 days was not anticipated to cause extra toxicity in the subset of patients we examined. LD ara-C has not been adopted universally, because some studies reported cytopenia. Although this may be a prerequisite for efficacy, our data do not indicate any excess toxicity or increased transfusion or other supportive care requirements compared with HU. Small nonrandomized studies in the literature suggest that between 10% and 20% of patients will achieve CR. This finding was reproduced in the current study. Although the number of patients with high-risk MDS that would have been defined as refractory anemia with excess blasts (RAEB) and RAEB in transformation was small, 1 of 5 patients achieved a CR. Among the patients with AML, 13 of 71 achieved CR, for an overall CR rate of 18%, whereas only 1 patient on the HU arm achieved CR. It is noteworthy that the time to CR was quite variable and could lend support to the argument supporting differentiation induction as the mechanism of response. Because patients were able to achieve CR, survival in the LD-Ara-C was highly significantly better than survival in the HU arm. Patients of all age groups derived benefit, but it was noticeable that no patient with adverse cytogenetics

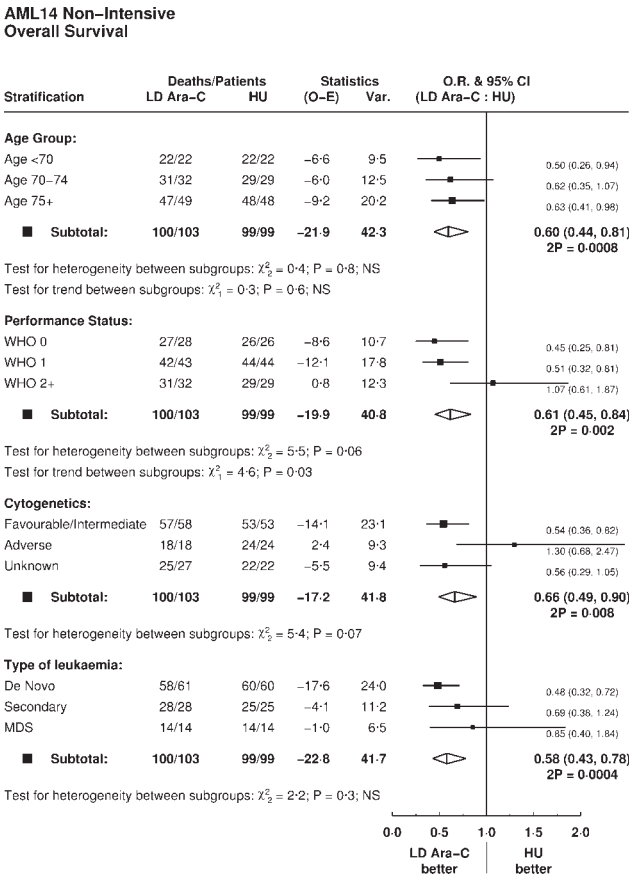


FIGURE 4. Stratified analyses of overall survival (ara-C vs HU randomization). WHO indicates World Health Organization; MDS, myelodysplastic syndrome; 2P, 2-sided.

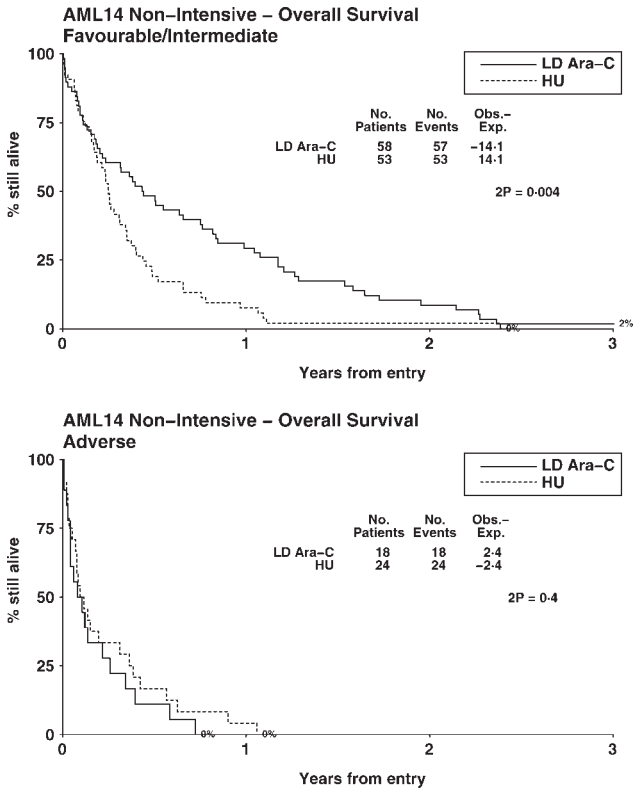


FIGURE 5. Overall survival by cytogenetic risk: LD ara-C versus HU; 2P, 2-sided.

achieved CR. We could find no evidence of benefit for patients unless they obtained CR, which is a well-established principle in AML treatment. Patients who achieved CR had a median survival of 80 weeks compared with 18 weeks if CR was not achieved.

The preclinical rationale for examining the addition of ATRA in this patient group was attractive. Because the overexpression of BCL-2 has been proposed as a mechanism of resistance to treatment and is relatively common in AML, the potential to improve sensitivity to ara-C or HU was worth testing. In vitro data also suggested that differentiation could be induced with ATRA in non-APL blasts. In the this study, we observed no effect from the addition of ATRA to either of the treatment arms. Other studies of ours are similarly negative with the sequencing that we used.

The basis on which patients are not considered fit for an intensive or a nonintensive approach to treatment is not clear. This is a well-recognized but ill-defined patient group. Traditionally, fitness or lack of fitness have been determined according to chronologic age, performance score, secondary disease, and the presence of comorbidity. In this trial, these characteristics are more frequent but are not exclusive to the patients who received the nonintensive approach. In addition, these characteristics do not seem to be sensitive enough on their own to dictate who may or may not benefit from a particular approach, so other parameters need to be identified that predict at diagnosis which patients are at risk of early mortality with an intensive treatment approach. Within this trial, it was clear from a multivariate analysis that a significant factor was the physician involved. Little work has been done in older patients with leukemia in this area, although various scoring systems are available in the elderly for other medical interventions. This issue will become even more relevant as this patient group is targeted as suitable for new drug development. In the absence of randomized data, it is not possible to be sure which approach is correct.

Although a very significant benefit in survival has been demonstrated with ara-C compared with HU, the outlook for patients who receive low-dose ara-C remains unsatisfactory. However, it can repre-

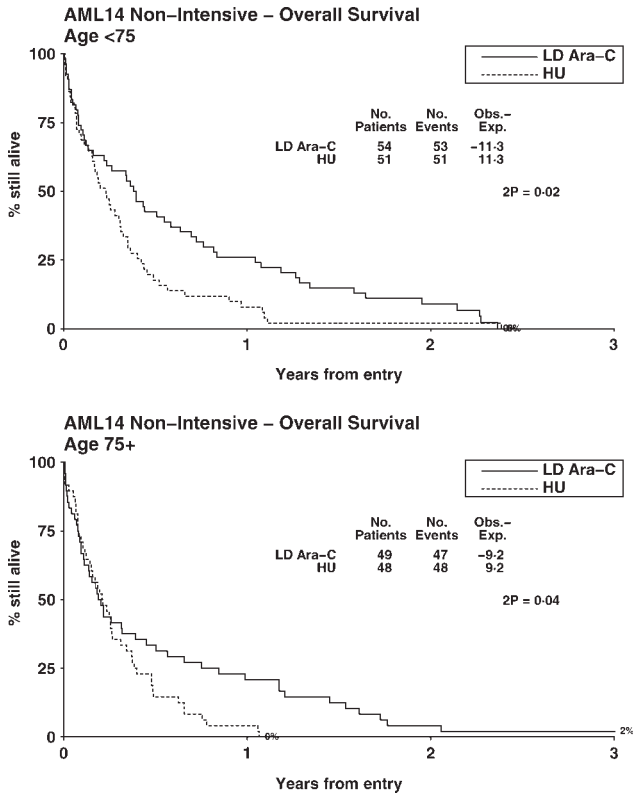


FIGURE 6. Overall survival by age: LD ara-C versus HU; 2P, 2-sided.

sent a baseline against which other promising treatments may be compared either alone or in addition to low-dose ara-C. Equally important will be the development of objective criteria with which to define patients who are *unfit for intensive treatment*. Some have suggested that this is defined as a 30% to 50% chance of mortality at 8 weeks and have presented prognostic factors that may define such patients.[24] This represents an important and growing subgroup of patients who have been neglected somewhat in trial protocols.

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