

Acute myelogenous leukaemia in older patients at St Bartholomew's Hospital: outcome with mitoxantrone and cytarabine

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Elderly patients (age >60 years) with AML who are selected for curative treatment frequently receive anthracycline/cytarabine containing regimens. The anthracendione mitoxantrone (MTN) in combination with cytarabine (Ara-C) produces comparable complete remission rates to other regimens and may be less toxic. Over a 12 year period, 75 patients (median age 67 years, range 60–83 years) referred with newly diagnosed AML were treated with MTN and ara-C. MTN was administered at 12 mg/m²/day intravenously for three days in the first 26 patients, and 10 mg/m²/day intravenously for five days in a subsequent 49 patients. Ara-C was administered at a dose of 100 mg/m² twice daily intravenously for seven days. Complete remission (CR) was achieved in 34 out of 75 patients (45%). The median disease-free survival overall was 7.5 months (one month to nine and a half years). The median survival was one year for patients in whom CR was achieved, compared to four months in patients whom treatment failed ($P=0.001$). Age alone was predictive of achievement of CR, whilst presentation karyotype, serum LDH and patient age correlated with overall survival. These results confirm that although elderly patients have a poor outcome, prognostic factors can be identified that influence treatment outcome in this important group of patients.

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Introduction

AML is predominantly a disease of the elderly with a median age at the time of presentation of 64 years.¹ The optimal clinical management of this group of patients remains controversial. Adverse host and disease specific factors such as presentation karyotype often contribute to a poor outcome in elderly patients who receive treatment with curative intent.^{2–4} However, prognostic data often utilized for treatment decisions for younger patients with AML are frequently ignored for elderly patients.

At St Bartholomew's Hospital, the anthracendione MTN in combination with ara-C superseded conventional '3+7' anthracycline/cytarabine curative therapy as the treatment of choice for AML in patients over 60 years of age in 1987. This change in treatment coincided with the introduction of routine cytogenetic analysis of AML cases at the time of presentation. The preliminary clinical outcome results from the first 33 patients who received this treatment at St Bartholomew's

in a prospective phase II study have been previously reported.⁵ The complete analysis, including cytogenetic data from all patients who received MTN/ara-C between July 1987 and December 1999 is presented below, together with prognostic data.

Materials and methods

Patients

From July 1987 to December 1999, 124 consecutive patients with newly diagnosed AML were referred to the ICRF. Department of Medical Oncology at St Bartholomew's Hospital. Seventy-five patients were selected for curative therapy with MTN/ara-C on clinical grounds and individual patient wishes, the remainder were managed conservatively with antibiotics and blood product support as appropriate. The clinical characteristics of patients included in the study are shown in Table 1.

Cytogenetic analysis

Standard cytogenetic analysis was performed (in the Medical Oncology Unit) using bone marrow or

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Table 1 Clinical and biological characteristics at presentation of 124 previously untreated patients with AML: comparison between active and symptomatic treatment

Parameters	Active treatment n = 75	Palliative/ symptomatic treatment n = 49	P-value
Age (years)			
Median	67	71	0.0009
Range	60–83	60–85	
Sex M:F	54:21	32:17	0.44
Blast count ($\times 10^9/l$)			
Median	2.35	0.95	0.55
Range	0–210	0–839	
Hb (g/dl)			
Median	9.1	8.45	0.40
Range	4.2–16.5	4.0–17.6	
WBC ($\times 10^9/l$)			
Median	15.05	6.2	0.15
Range	0.8–316	0.5–475	
Platelets ($\times 10^9/l$)			
Median	46	44	0.89
Range	8–299	7–215	
LDH			
Median(U/l)	560	2964	0.18
Range	210–5658	451–4750	
Albumin (g/l)			
Median	38	36	0.006
Range	26–49	25–44	
FAB M0	1	2	0.01
M1	32	11	
M2	16	9	
M3	2	3	
M4	12	9	
M5	8	0	
M6	3	4	
M7	0	0	
Secondary AML	1	2	
Hypoplastic AML	0	3	
Antecedent	23	20	0.33
haematological disorder			
Hepatomegaly alone	5	9	
Splenomegaly alone	7	1	0.10
Hepatosplenomegaly	11	8	
Neither	52	29	

peripheral blood from patients at the time of diagnosis. Short-term cultures were established using complete medium (RPMI 1640 with glutamax, 20% fetal calf serum, 1% Streptomycin and Penicillin). Metaphase preparations were harvested, and GTG banding performed.⁶ Patient karyotypes were described according to the International System For Human Cytogenetic Nomenclature (ISCN).⁷

Treatment

Mitoxantrone was initially administered at 12 mg/m² intravenously for three days and Ara-C at 100 mg/m² twice daily, intravenously, for 7 days to 26 patients. Due to a high early recurrence rate, subsequent patients ($n=49$) received MTN at 10 mg/m² intravenously for five days with the same dose schedule for ara-C.⁵

The aim was to administer a total of four cycles of treatment irrespective of the number of cycles required to achieve CR.

Supportive care

Neutropenic fever was initially treated with aminoglycoside and broad-spectrum cephalosporin antibiotic combinations. Systemic antifungal therapy was administered in addition to broad spectrum antibiotics in patients who remained febrile for more than 72 h or earlier if clinical suspicion was high. Granulocyte and granulocyte-macrophage colony-stimulating factors were not routinely used as an adjunct to the management of neutropenic fever. Prophylactic platelet and red cell transfusions were administered to maintain counts above $10 \times 10^9/l$ and 10 g/dl respectively.

Definitions

The morphological diagnosis of AML was made according to the French American British classification of acute leukaemia.^{8–11} The presence of coexisting trilineage myelodysplasia with *de novo* AML was determined according to recognized criteria.¹²

Complete remission (CR) was defined as having been achieved when the patient was well, in the presence of normocellular bone marrow containing less than 5% blast cells, together with peripheral blood counts demonstrating Hb > 10 g/dl, neutrophils > $1 \times 10^9/l$ and platelets > $100 \times 10^9/l$. Patients were classified as having 'resistant disease' (RD) if there was either no change or an increase in the percentage of leukaemic blast infiltration at the time of evaluation after two cycles of treatment. Patients who did not achieve CR because of a hypocellular bone marrow or peripheral blood cytopenia, despite the absence of leukaemic bone marrow infiltration were also included in this group. Deaths attributable to organ failure, infection or bleeding during the first two cycles of chemotherapy, in the absence of resistant disease, were defined as treatment-related death (TRD).

Statistical methods

Potential prognostic markers for survival were assessed using a log-rank test, with multivariate analysis performed using Cox regression. For achievement of CR, the same factors were assessed using logistic regression. The comparatively small number of patients with resistant disease made the derivation of a multivariable prognostic model for this outcome unfeasible. Therefore, univariate analysis was used to analyse potential factors for resistant disease. For categorical variables, this was performed using Fisher's exact test, whilst a Mann–Whitney test was used to investigate the equality of the distributions of continuous measurements between patients with and without resistant disease. Analyses of all cytogenetic data tables were performed by exact or Monte-Carlo methods. The natural ordering of all ordered categorical variables (e.g. age group) was preserved by using an 'exact' version of the Kruskal–Wallis test (for singly-ordered tables) or the Jonckheere–Terpstra test

(for doubly-ordered tables) as appropriate, otherwise Fisher's test was used.

Results

Patient characteristics

Patients who received treatment with curative intent were significantly younger, and had significantly higher serum albumin concentrations than patients who were managed conservatively. Comparisons between all other clinical and laboratory parameters were similar when the patients from the two treatment groups were compared (Table 1).

Cytogenetics

Cytogenetic analysis was performed using bone marrow or peripheral blood from 108 out of 124 patients who were eligible for treatment with mitoxantrone/cytarabine. Successful cytogenetic results were obtained in 95% of cases, normal karyotype was noted in 44% of all patients. In patients who received chemotherapy with curative intent, a normal karyotype was seen in 49% of patients, whilst in patients who were managed conservatively only 34% showed abnormal karyotype.

Modal number Pseudodiploidy was found in 17% of patients, 20% of patients were hypodiploid: of these, 14 had 45 chromosomes, six cases had 44 chromosomes, and the remaining two cases had 43 and 42 chromosomes respectively. In most patients with 45 chromosomes, hypodiploidy was the result of monosomy 7 ($n=7$) or monosomy 5 ($n=5$).

Numerical chromosomal aberrations The most frequent numerical aberrations included monosomy 5, trisomy 8 and monosomy 7. Monosomy 7 was noted in 9% of patients, and was the sole abnormality in 3%. The remaining patients had complex karyotypes that included monosomy 5 and other numerical and structural. Abnormalities resulting in complete or partial deletion of chromosome 5 were associated with complex karyotypes and occurred in 10 and 7% of patients respectively. An extra copy of chromosome 8 was observed in 11% of patients, and was the sole abnormality in 3%. The acquisition of an extra copy of chromosome 21 occurred in 4% patients and in 3 out of 4 of these patients was associated with other chromosomal aberrations.

Recurrent chromosomal translocations Non-random translocations normally associated with *de novo* AML were less frequent than numerical aberrations; $t(8;21)$ 3%, $t(15;17)$ 3%, $inv(16)$ 2%). In the three patients with the $t(8;21)(q22;q22)$ translocation, one was pseudodiploid, whilst the remaining two patients had 47 and 45 chromosomes as a result of trisomy 8 and loss of the Y chromosome respectively. The

$t(15;17)(q22;q21)$ translocation was found in three patients, two of whom had an extra copy of chromosome 8. The $inv(16)(p13q22)$ rearrangement was noted in two patients, both of which were pseudodiploid.

Presentation karyotype and prognostic sub-groups For the purposes of clinical outcome, patients were divided into three cytogenetic sub-groups retrospectively based on previously defined MRC prognostic criteria:¹³ (1) 'favourable' ($t(8;21)$, $t(15;17)$, $inv(16)$), (2) 'unfavourable' ($-5/5q-$, -7 , and complex karyotype (three or more distinct chromosomal rearrangements)), (3) 'intermediate' (miscellaneous cytogenetic aberrations or normal karyotype) (Table 2).

Presentation karyotypes consistent with an 'intermediate' prognosis were the most frequent prognostic sub-group in patients who received treatment with curative intent, accounting for 75% of cytogenetic results. 'Unfavourable' chromosomal aberrations were the second most frequent cytogenetic sub-group in patients managed with curative intent accounting for 14%, whilst 'favourable' karyotype accounted for 11%. The distribution of the cytogenetic prognostic sub-groups between the patients who were treated with curative intent and those who were managed conservatively was statistically different ($P=0.003$), with patients who received curative therapy having significantly higher frequency of favourable karyotypes compared to patients who were managed conservatively.

Cytogenetic sub-group and patient age When patients were stratified according to age, chromosomal aberrations associated with 'intermediate' prognosis were the most common category in each age group (Table 3). 'Favourable' karyotypes were the least frequent sub-group overall, accounting for 11% in patients up to the age of 70 years, and 0% in those over 70 years of age. There was a trend toward an increase in the frequency of 'unfavourable' cytogenetic aberrations with increas-

Table 2 Cytogenetic prognostic sub-group at presentation: comparison between elderly patients receiving curative therapy and elderly patients treated conservatively

Prognostic group	Curative chemotherapy		Conservative treatment		Total n
	n	(%)	n	(%)	
Favourable ^{a,b}	7	(11)	1	(3)	8
Unfavourable ^{a,b}	9	(14)	16	(42)	25
Intermediate ^a	49	(75)	21	(55)	70
(Normal ^b)	32	(49)	13	(34)	45
(Miscellaneous ^b)	17	(26)	8	(21)	25
Total	65		38		103

Key: 'Favourable' group: $t(8;21)$, $t(15;17)$, $inv(16)$. 'Unfavourable' group: $-5/5q-$, -7 , complex karyotype (3 or more distinct chromosomal rearrangements). 'Intermediate' group: other chromosomal abnormalities (miscellaneous) and normal karyotype. ^aDistribution of cytogenetic sub-groups (favourable, unfavourable and intermediate) between two patient groups $P=0.003$. ^bDistribution of cytogenetic sub-groups (favourable, unfavourable, miscellaneous and normal) between the two patient groups $P=0.01$.

ing age. For patients aged 60–65 years, ‘unfavourable’ karyotypes were noted in 19%, and the incidence rose to 43% of karyotypes in patients over 76 years old. The frequency of complete or partial deletion of chromosome 5, and monosomy 7 showed no discernible relationship with patient age (Table 4). Younger patients were more likely to have presentation karyotypes with one or two distinct cytogenetic aberrations, whilst older patients had a tendency to present with three or more cytogenetic aberrations ($P=0.02$). Thus increasing patient age was associated with an ‘unfavourable’ karyotype due to complex chromosomal aberrations.

Clinical outcome

Response to treatment Complete remission (CR) was achieved in 34 out of 75 (45%) patients who received MTN/ara-C. However, taking into account patients who were ineligible for curative therapy the ‘real’ CR rate was only 27%. Seventy-six per cent of patients who entered CR did so with the first course of therapy. Twenty-one per cent of patients in whom CR was achieved received no further treatment due to general debility and septic complications incurred as a consequence of the first cycle of chemotherapy. Only 5 out of 24 of the remaining patients received

two or three courses of consolidation chemotherapy, whilst only 4% of patients treated with curative intent received the desired four courses of chemotherapy.

There was a trend toward a lower CR rate with increasing patient age, being 59% in those under 66 years and 39% in those patients older than 70 years of age. Factors predictive of CR on univariate analysis included presentation karyotype, serum lactate dehydrogenase (LDH), and presence of hepatosplenomegaly (Table 5). Patients with ‘favourable’ and ‘normal’ karyotype had a significantly higher CR rate compared to those with ‘unfavourable karyotype’ (71 vs 22%; $P=0.05$), and (50 vs 22%; $P=0.04$), however, there was no significant difference between the CR rates of patients with ‘intermediate’ and ‘unfavourable’ karyotype (45 vs 22%; $P=0.20$). Serum LDH was available on 44 patients who received therapy. The median LDH for patients who achieved CR was 559 (normal range <480 IU/l), compared to 755 in patients where treatment failed. Patients with serum LDH <twice upper limit of normal ($n=32$) had a significantly higher CR rate than patients with LDH >twice upper limit of normal ($n=12$) (86 vs 14%; $P=0.04$). Likewise patients without hepatosplenomegaly ($n=52$) had a significantly better CR than patients with hepatosplenomegaly ($n=10$) (52 vs 10%; $P=0.01$). By multivariate analysis, increasing patient age was the only factor predictive of

Table 3 Patient age in relation to cytogenetic sub-group

Prognostic group	Age (years)								Total
	60–65		66–70		71–75		>76		
Favourable	4	(11)	4	(11)	0	–	0	–	8
Unfavourable	7	(19)	9	(26)	6	(25)	3	(43)	25
Intermediate	26	(70)	22	(63)	18	(75)	4	(57)	70
Normal	12	(32)	16	(46)	15	(63)	2	(29)	45
Miscellaneous	14	(38)	6	(17)	3	(13)	2	(29)	25
Total	37		35		24		7		103

Table 4 Karyotypic patterns and specific chromosomal aberrations in AML in relation to patient age

	Age (years)								P-value
	60–65 n=37		66–70 n=35		71–75 n=24		>76 n=7		
Normal	12	(32)	16	(46)	15	(62)	2	(29)	0.10
Abnormal	25	(68)	19	(54)	9	(38)	5	(71)	
1 anomaly	15	(40)	10	(28)	4	(17)	1	(14)	
2 anomalies	5	(14)	1	(3)	1	(4)	0	0	
≥3 anomalies	5	(14)	8	(23)	4	(17)	4	(57)	
t(8;21)	1	(3)	2	(5)	0	0	0	0	
t(15;17)	2	(5)	1	(3)	0	0	0	0	
inv(16)	1	(3)	1	(3)	0	0	0	0	
Total	4	(11)	4	(11)	0	0	0	0	
–5	2	(5)	5	(14)	3	(13)	0	(0)	
5q–	1	(3)	3	(9)	1	(4)	2	(29)	0.14
–7	4	(11)	1	(3)	3	(13)	1	(14)	0.84
7q–	1	(3)	3	(9)	0	0	1	(14)	0.74
3q	1	(3)	0	0	0	0	0	0	0.43
Total	9	(24)	12	(34)	7	(29)	4	(57)	

Table 5 Prognostic factors for achievement of complete remission and overall survival for patients treated with mitoxantrone and cytarabine

<i>Complete Remission</i>		<i>P value</i>	
<i>Univariate analysis</i>			
LDH < twice upper limit of normal			0.04
Cytogenetic sub-group			0.05
Hepatosplenomegaly			0.008
<i>Multivariate analysis</i>			
	<i>OR</i>	<i>95% Confidence Interval</i>	<i>P value</i>
Age/(5 year increment)	0.30	0.11–0.82	0.02
LDH < twice upper limit of normal	4.07	0.66–25	0.13
<i>Cytogenetic sub-group^a</i>			
<i>(base line: Normal)</i>			
Miscellaneous	0.35	0.08–1.46	0.15
Unfavourable	0.17	0.03–1.06	0.06
Favourable	1.33	0.20–8.61	0.77
<i>Overall Survival</i>			
<i>Univariate analysis</i>			
LDH < twice upper limit of normal			0.002
Cytogenetic sub-group			0.04
<i>Multivariate analysis</i>			
	<i>HR</i>	<i>95% Confidence Interval</i>	<i>P value</i>
LDH < twice upper limit of normal	0.32	0.14–0.70	0.005
Age/(5 year increment)	1.56	1.03–2.37	0.04
<i>Cytogenetic sub-group</i>			
<i>(base line: Normal)</i>			
Miscellaneous	1.04	0.48–2.28	0.92
Unfavourable	3.58	1.24–10.3	0.02
Favourable	0.29	0.06–1.47	0.13

Key: Odds ratio, OR < 1 indicates greater probability of achieving complete remission. Hazard ratio, HR < 1 indicates a poorer overall survival.
^aMultivariate analysis if LDH excluded.

a reduced likelihood of achieving CR although ‘unfavourable’ karyotype was also predictive of this if serum LDH was excluded from the analysis (odds ratio 0.3, $P=0.02$; odds ratio 0.17, $P=0.06$ respectively) (Table 5).

For patients who entered CR, the median disease-free survival (DFS) was seven and a half months (one month to nine and a half years). Although patients with ‘favourable’ karyotype were noted to have the longest duration of remission at 15 months (range six months to nine and a half years) statistical analysis failed to identify an association between DFS and patient karyotype or any other laboratory or clinical parameters.

Treatment failure due to resistant disease (RD) occurred in 20% of patients who received curative therapy, of these, 11 patients had persistent leukaemic bone marrow infiltration after therapy, the remaining four patients failed to recover normal blood counts due to persistent hypocellular bone marrow. Resistant disease occurred more frequently in patients with ‘unfavourable’ karyotype (44%) than in the two remaining prognostic cytogenetic sub-groups. Patients with ‘favourable’ karyotype did not demonstrate resistant disease, whilst patients with normal karyotype and miscellaneous cytogenetic aberrations had a similar rate of RD at 19 and 18% respectively. Although the difference in RD in the three sub-groups appeared appreciable it was not found to be statistically significant.

Treatment-related deaths (TRD) were noted in 28% of patients who received MTN/ara-C (16 from sepsis, two from renal failure, one from cerebral haemorrhage, one from intestinal infarction, one from heart failure). Four patients died in CR whilst receiving consolidation chemotherapy, of these two were treatment-related deaths. Three patients had morphological evidence of myelodysplasia after completion of therapy, these cases were considered to be treatment failures, and were not defined as resistant disease.

Survival With a median follow up of 5.5 years, actuarial survival for treated patients at one, three and five years was 33, 10 and 7% respectively. Median survival from the time of diagnosis was six months (Figure 1). For patients treated with curative intent who achieved CR, median survival was significantly better than in those in whom treatment failed, (12 months vs four months; $P=0.01$). Not surprisingly, the overall survival (OS) of patients who received MTN/ara-C was significantly better than that of patients who were managed conservatively (three months vs one month; $P=0.0001$). Importantly, the OS of patients with ‘unfavourable’ cytogenetic subtype who received curative treatment, at one month, was identical to that of patients managed conservatively. There was no difference between the OS of the 26 patients who received MTN at 12 mg/m² for three days and that of the 49 patients who received MTN at 10 mg/m² for five days.

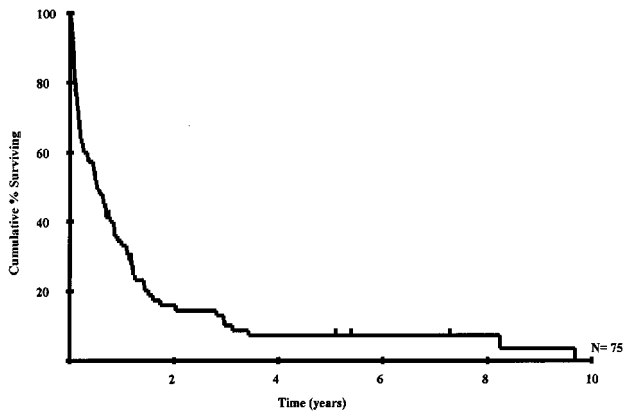


Figure 1 Kaplan–Meier survival curve for patients aged 60 years and above with AML treated with Mitoxantrine and Cytarabine.

Long term survival (greater than five years) was noted in only four out of 124 patients, three had ‘favourable’ karyotypes the remaining patient had an ‘intermediate’ karyotype with miscellaneous chromosomal aberrations. One patient relapsed whilst in first remission at eight months and subsequently entered second remission having received further chemotherapy and is currently alive in second CR. Two of the remaining patients died of pneumonia and carcinoma of the lung respectively, whilst in first CR at eight and eight and a half years respectively.

Factors predictive of OS on univariate analysis included presentation karyotype and serum LDH (Table 5). Patients in ‘favourable’ and ‘intermediate’ cytogenetic sub-groups had a better OS compared to that of patients with ‘unfavourable’ karyotypes (10 months *vs* one month; $P=0.004$), (six months *vs* one month; $P=0.03$) respectively. Patients with ‘favourable’ karyotypes also had a significantly better OS than patients with ‘intermediate’ karyotypes ($P=0.05$). Within the ‘intermediate’ group, there was no difference in the OS of patients with normal karyotype compared to patients with miscellaneous aberrations (Figure 2). The overall survival of patients with serum LDH at presentation $<$ twice upper limit of normal was significantly better than the OS of patients with serum LDH $>$ twice normal at presentation (10 months *vs* one and a quarter months; $P=0.002$). Presentation karyotype and serum LDH remained predictive for OS on multivariate analysis, but in addition to these co-variables, patient age was also found to be predictive for OS (Table 5).

Haematological toxicity The median time to recover neutrophils $>0.5 \times 10^9/l$ and platelet $>50 \times 10^9/l$ after chemotherapy was similar at 26 days and 25 days respectively. Patients who received MTN at 12 mg/m² daily for three days had shorter median recovery times compared to patients who received MTN at 10 mg/m² daily for five days (23 days *vs* 29 days and 21 days *vs* 37 days respectively).

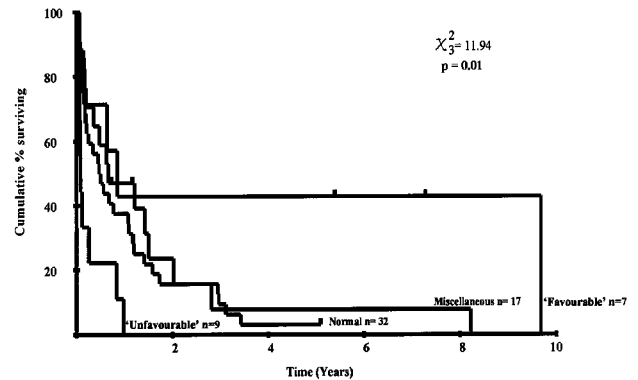


Figure 2 Kaplan–Meier survival curve for patients aged 60 years and above with AML treated with Mitoxantrine and Cytarabine, according to cytogenetic sub-group (‘Favourable’ group: t(8;21), t(15;17), inv(16), ‘Unfavourable’ group: -5/5q-, -7, complex karyotype (three or more distinct chromosomal rearrangements), ‘Intermediate’ group: other chromosomal abnormalities (miscellaneous) and normal karyotype).

Conclusion

Clinical outcome data for elderly patients with AML is frequently disappointing due to low complete remission rates, higher attendant resistant disease and treatment related mortality. Thus for many physicians, the decision to treat elderly patients with this disease using aggressive ‘curative’ therapy is often based upon subjective criteria, including the ability to withstand the treatment, rather than utilizing objective prognostic data that may correlate with treatment outcome. In this study, clinical outcome for selected older patients with AML in terms of complete remission and overall survival was shown to correlate with presentation karyotype, as well as other factors such as patient age and serum LDH at presentation. Although the number of patients in the study may have limited the statistical power of the prognostic sub-groups, by utilizing presentation karyotype, patients with favourable karyotype were defined by CR rates comparable to those quoted for younger adults with AML, whilst patients with unfavourable karyotype had clinical outcome no better than individuals who received supportive care alone. Furthermore resistant disease was found to correlate with unfavourable karyotype. Similar results have been reported by other groups, including a large series recently published by the MRC group.¹⁴ Thus, although treatment outcome is frequently disappointing in older patients, presentation karyotype can be used to ‘risk stratify’ patients, and identify those individuals who may benefit from either aggressive chemotherapy, or conversely a more conservative management strategy.

Cytogenetic data is not always readily available at the time of diagnosis, and a delay in initiating therapy may be incurred if bone marrow karyotype results are waited for. However, other prognostic data can be used to stratify clinical outcome, as we have shown. Importantly patient age remains a significant prognostic factor, influencing both CR and OS. However,

elevated serum LDH was also predictive of reduced OS in keeping with other studies.³ These data are readily available to the physician at the time of presentation and their judicious use, either alone or together with cytogenetic data, may facilitate a more objective decision making process for this group of patients. Indeed scoring systems have been derived from prognostic factors identified in multivariate analysis in other studies. In one such model, performance status, peripheral blood count, hepatomegaly and blood urea were found to predict for survival,¹⁵ whilst serum LDH and presentation karyotype were successfully used as a way of objectively selecting elderly

patients for aggressive chemotherapy by another group.¹⁶ The development and validation of a prognostic scoring system was not an aim of this study. However, given the potential problems that face elderly patients, and their physicians when curative treatment is administered, a greater appreciation of prognostic factors that influence outcome should be encouraged.

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