



THERAPY OF ACUTE MYELOID LEUKEMIA

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Introduction

Approximately 50%-75% of adults with acute myeloid leukemia (AML) achieve complete remission (CR) with an anthracycline and cytarabine.¹⁻⁵ However, long-term disease-free survival (DFS) occurs in only 20%-30% of patients who achieve CR. The majority of patients with AML still die of their disease.

The Eastern Cooperative Oncology Group (ECOG) has recently reviewed the outcome for more than 1,400 patients with previously untreated AML entered on five successive clinical trials.^{5,6} Each trial included daunorubicin and cytarabine for induction. Successive trials in this analysis included postremission therapy with increasingly more intensive consolidation. Among 1,414 patients, 62% achieved CR, but 76% have relapsed or died. The overall survival (OS) rate for all patients at 5 years is only 15%. Patients aged 55 years or older fared particularly poorly. The 5-year OS rate was 9%-33% for patients less than 55 years of age and 6%-15% for patients aged 55 years and older.^{5,6} Among patients less than age 55 years, both the DFS and OS increased with more intensive postremission strategies.

The outcome for adults with AML depends on several factors: the age of the patient, the intensity of postremission therapy, and the biologic characteristics of the disease, including karyotype and expression of the multidrug resistant (MDR) phenotype. The French-

American-British (FAB) classification has been widely adopted and has promoted uniformity of diagnosis of morphologic subtypes of AML.⁷ It remains useful in identifying certain biologic subtypes but does not, by itself, account for all subtypes. The diagnosis and prognosis is based not only on the FAB classification, but also on cytogenetics, immunophenotyping, and molecular genetics. Such advances have led to a new proposed World Health Organization classification that attempts to correlate morphology, cytochemistry, immunophenotype, karyotype, and molecular genetics with clinical features.⁸ Several host-related and disease-related factors have prognostic importance including age older than 60 years, the presence of an antecedent myelodysplastic syndrome, elevated white blood cell count, karyotype, and expression of the MDR phenotype.⁹⁻¹⁸ The initial karyotype has emerged as one of the most important independent prognostic factors and can distinguish three groups with prognostic value (Fig 1): (1) favorable: t(15;17), t(8;21), inv(16), (2) intermediate: normal karyotype, trisomy 8, 11q23, del(7q), del(9q), trisomy 22, other numerical abnormalities, or (3) adverse: complex karyotype, -7, -5, del(5q), abn(3q).^{13,17} However, such classifications do not completely account for karyotypes with multiple abnormalities, each with its independent prognostic value,^{19,20} the importance of molecular detection of specific abnormalities and variants,²¹⁻²³ or the potential influence of associated antigen expression.²⁴ Advances in outcome have occurred primarily in supportive

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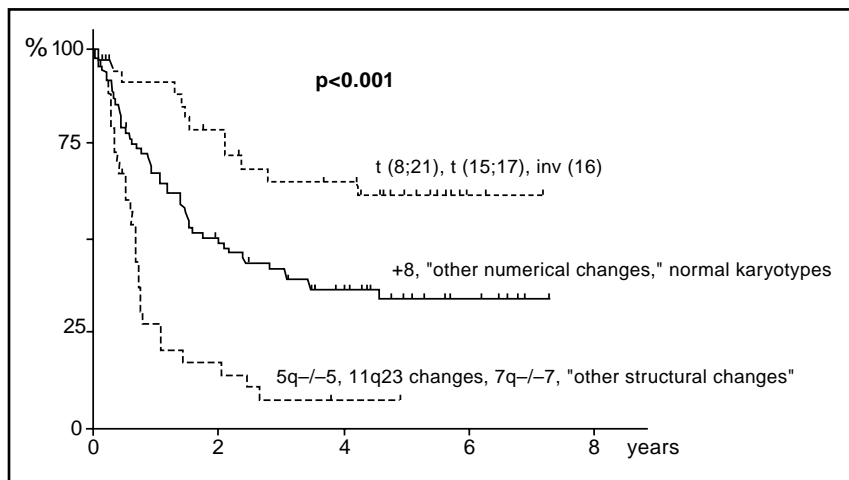


Fig 1. — Probability of continuous complete remission of previously untreated patients with AML according to chromosomal groups. From Dastague N, Payen C, Lafage-Pachitaloff M, et al. Prognostic significance of karyotype in de novo adult acute myeloid leukemia. The BGMT group. *Leukemia*. 1995;9:1491-1498. Reprinted with permission.

days.^{1,29} Daunorubicin at a dose of 30 mg/m² proved to be inferior to 45 mg/m² in patients less than 60 years of age and less toxic than 30 mg/m² of doxorubicin.² Finally, 100 mg/m² of cytarabine was found to be equally effective as 200 mg/m².³⁰ Therefore, the most widely used combination for induction chemotherapy today is daunorubicin at 45 mg/m² per day intravenously (IV) for 3 days, cytarabine at 100 mg/m² per day IV for 3 days, and cytarabine 100 mg/m² by continuous IV infusion for 7 days.

A number of studies have been conducted recently to improve the CR rate. Some trials have tested new agents such as etoposide or high-dose cytarabine (HiDAC).³¹

Anthracyclines in Induction Therapy

The anthracyclines include daunorubicin, doxorubicin, aclarubicin, the synthetic anthracenedione, mitoxantrone, and the synthetic agent 4-demethoxydaunorubicin (idarubicin). Idarubicin may be better as an induction agent

care,²⁵ in increased intensity of postremission chemotherapy,⁶ and in bone marrow (stem cell) transplantation.

Induction Chemotherapy

During the past 30 years, a series of studies has identified an induction regimen that is considered standard. Approximately 30%

40% of patients achieve CR with either cytarabine or daunorubicin given as a single agent.²⁶⁻²⁸ CR was achieved in more than 50% of patients when these agents were combined. The Cancer and Leukemia Group B established that a regimen of 3 days of daunorubicin and 7 days of cytarabine was better than 2 days and 5 days, respectively, and that 10 days of cytarabine was not better than 7

Table 1. — Randomized Trials of Idarubicin (I) vs Daunorubicin (D)

Author	Number of Patients		Median Age (years)		CR Rate (%)			CR Cycle 1 (%)		Resistant Leukemia (%)		Median OS (months)		
	I	D	I	D	I	D	P value	I	D	I	D	I	D	P value
Berman ³⁶	60	60	36	41	80	58	.005	75	49	8	21	20	14	.025
Wiernik ³⁷	97	111	56	55	70	59	.08	55	38	6	22	13	9	.038
Vogler ³⁸	105	113	60	61	71	58	.03	77	78	10	18	11	9	.0913
Mandelli ³⁹	124	125	63	62	40	39	NA	74	51	14	31	3	6	.23

CR = complete remission
OS = overall survival
NA = not available

because of its higher lipid solubility, increased cellular uptake, induction of more DNA single-strand breaks, conversion to an alcoholic derivative (13-hydroxyidarubicin, an active metabolite with a prolonged plasma half-life), greater toxicity of AML blast cells, and less dependency on P-glycoprotein efflux.³²⁻³⁵

Four prospective randomized trials comparing idarubicin to daunorubicin suggest that idarubicin may have benefits, particularly in young adults (Table 1).³⁶⁻³⁹ In three of the studies, idarubicin was associated with a significantly higher CR rate, particularly in younger patients, was more effective in eradicating leukemia after one course, and was associated with a lower incidence of resistant leukemia. The study by Mandelli and colleagues³⁹ for the Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto (GIMEMA) was the only trial that did not show a higher CR rate with idarubicin. This trial included patients with preexisting myelodysplasia who were excluded by Berman and colleagues.³⁶ Although patients with an antecedent myelodysplastic syndrome were eligible in the studies by Wiernik et al³⁷ and Vogler et al,³⁸ few such patients were included. The GIMEMA study³⁹ included only patients older than 55 years of age, whereas the other two studies did not restrict the upper age limit. The CR rate with idarubicin was not unfavorably influenced by hyperleukocytosis in the studies by Berman and colleagues³⁶ and Wiernik et al³⁷ but it was with daunorubicin.

Higher CR rates have been achieved with idarubicin compared to daunorubicin in younger patients. Idarubicin may be beneficial in patients presenting with hyperleukocytosis. In these prospective studies, idarubicin at either 12 or 13 mg/m² was compared to daunorubicin at a dose of 45 mg/m². Therefore, it may be possible that a higher dose of daunorubicin may confer the same apparent benefits observed with idarubicin. A prospective randomized trial has not been conducted that compares daunorubicin at a dose of 45 mg/m² to either 60 mg/m² or 70 mg/m². Furthermore, it is not clear that OS with idarubicin is superior to that

achieved with daunorubicin since two studies showed an advantage and two did not. A meta-analysis by the AML Collaborative Group⁴⁰ reported similar early induction failure rates (20% for idarubicin vs 18% for daunorubicin, $P=0.4$), but fewer late (after day 40) induction failures with idarubicin (62% vs 53%, $P=0.002$). Among patients achieving CR, fewer patients assigned to idarubicin relapsed ($P=0.008$) but somewhat more died in CR, resulting in a nonsignificant benefit in DFS ($P=0.07$). OS was better with idarubicin compared with daunorubicin, with 13% vs 9%, respectively, alive at 5 years ($P=0.03$) (Table 2). Therefore, there is level 1, grade

Table 2. — Daunorubicin vs Idarubicin in Induction in AML

Outcome	Treatment		NNT or NNH (95% CI)	ARR (95% CI)	RRR (95% CI)
	Daunorubicin (n = 521)	Idarubicin (n = 532)			
Complete Remission	53%	62%	11 7 to 3	9% 3% to 15%	17% 5% to 29%
Early Death	18%	20%	50 15 to -37*	2% -3%* to 7%	
Late Failure	29%	17%	8 6 to 14	12%** 7% to 17%	
Level of Evidence/Grade	1, meta-analysis/A				

* Minus sign (-) denotes that daunorubicin may be more toxic (ie, NNH ranges from $NNH_{IDA}15$ to ∞ to $NNH_{DAU}37$).

** Daunorubicin has more late failures.

NNT = number needed to treat to avoid 1 adverse outcome
 NNH = number needed to treat to harm 1 individual
 CI = confidence interval
 RRR = relative risk reduction
 ARR = absolute risk reduction

Data from the AML Collaborative Group. A systematic collaborative overview of randomized trials comparing idarubicin with daunorubicin (or other anthracyclines) as induction therapy for acute myeloid leukaemia. *Br J Haematol.* 1998;103:100-109. Published by Blackwell Science Ltd, Oxford, UK.

Table 3. — Levels of Evidence and Grades of Recommendations

Level of Evidence	Description	Grade of Recommendation
1	Meta-analyses or individual randomized trials in which the lower limit of the confidence interval for the treatment effect exceeds the minimal clinically important benefit	A
2	Meta-analyses or individual randomized trials in which the lower limit of the confidence interval for the treatment effect exceeds the minimal clinically important benefit	B
3	Nonrandomized concurrent cohort studies	C
4	Nonrandomized historic cohort studies	C
5	Case-series	C

From Sacket DL. Science for the art of consensus. *J Natl Cancer Inst.* 1997;89:1003-1005. Reprinted with permission.

A evidence (Table 3) that, in younger patients, idarubicin is superior to daunorubicin.

Mitoxantrone is associated with a relatively steep dose-response rate in clonogenic assays of leukemia cells and has a favorable extramedullary toxicity profile.⁴¹ Mitoxantrone^{42,44} and aclarubicin,⁴⁵ a class III anthracycline whose uptake and outward transport is largely unaffected in MDR cell lines, may also offer advantages. In the studies reported to date, mitoxantrone appears at least as effective and aclarubicin more effective than daunorubicin in younger patients with respect to CR rate but not OS, and both may be associated with less-resistant leukemia.

In a comparative trial,⁴⁶ cytarabine and 6-thioguanine were combined with amsacrine (a DNA inter-

calator distinct from anthracyclines) or 50 mg/m² of daunorubicin. Amsacrine given with cytarabine and 6-thioguanine was associated with a higher CR rate compared with daunorubicin (70% vs 54%, $P=0.03$), more frequent achievement of CR with only one cycle (48% vs 28%, $P=0.03$), and improved OS ($P=0.01$).

Several other studies have addressed the dose and choice of anthracyclines specifically in older adults. Buchner and colleagues⁴⁷ compared daunorubicin at 30 mg/m² and at 60 mg/m² during induction in patients older than 60 years of age, followed by consolidation and monthly maintenance for 3 years. The CR rate was higher among patients receiving the larger dose (52% vs 45%, $P=0.026$), and it was higher after one cycle (38% vs 20%, $P=0.001$). Survival was significantly improved only among

patients older than age 65 (14% vs 5%, $P=0.002$). A small trial by Feldman and colleagues⁴⁸ compared mitoxantrone at 80 mg/m² given once (high-dose) with 36 mg/m² given over 3 days (standard-dose). CR was achieved in 57% of patients on the high-dose arm compared with 43% on the standard-dose arm. However, the median time to relapse was 6 months, and there was neither a statistically significant difference between the two groups nor a difference in toxicity.

ECOG has completed a prospective randomized trial in older adults of daunorubicin vs idarubicin vs mitoxantrone as the anthracycline given with cytarabine.⁴⁹ A total of 350 evaluable patients were accrued. A preliminary analysis shows that the CR rates achieved with the three different anthracyclines did not differ. There was a trend toward a decreased induction mortality rate on the mitoxantrone arm. In the collaborative trial of the European Organization for Research and Treatment of Cancer (EORTC) and the Dutch-Belgian Hemato-Oncology Cooperative Group (HOVON),⁵⁰ patients 60 years of age and older were randomized to receive either 30 mg/m² of daunorubicin for 3 days or 8 mg/m² of mitoxantrone for 3 days plus cytarabine 100 mg/m² by continuous infusion for 7 days. There was a modestly higher CR rate with mitoxantrone compared with daunorubicin (46.6% vs 38.0%, $P=.067$) that was likely related to a reduced probability of resistant leukemia (47% vs 32%, $P=.001$) since the induction mortality was somewhat higher with mitox-

Table 4. — Randomized Studies of HiDAC (H) vs Standard-Dose Cytarabine (S) in Induction in AML

Author	Number of Patients		Complete Remission (%)			5-Year Disease-Free Survival (%)			5-Year Overall Survival (%)		
	S	H	S	H	P value	S	H	P value	S	H	P value
Weick ⁵⁵	493	172	58	55	.96	21	33	.049	22	32	.41
Bishop ⁵⁴	152	149	74	71	.70	23	41	.007	25	31	.44
Schiller ⁵³	51	50	71	74	.90	20	28	.90	25	37	.90

HiDAC = high-dose cytosine arabinoside

antrone (21% vs 15%). However, among patients who achieved CR, there was no difference in DFS or OS. In the Medical Research Council (MRC) AML-12 trial,⁵¹ 1,243 patients aged 15 to 59 years (26 patients between 60-65 years of age) were randomly assigned either daunorubicin or mitoxantrone, each given cytarabine for one or two courses for induction. All patients achieving CR subsequently received multiple courses of consolidation chemotherapy. There were no significant differences in CR, percentage of patients dying in CR, resistant disease, relapse, DFS, or OS between the two induction regimens. The EORTC and GIMEMA conducted a prospective trial of either daunorubicin, mitoxantrone, or idarubicin combined with cytarabine and etoposide in standard doses for induction in younger patients followed by 500 mg/m² of cytarabine every 12 hours for 6 days plus the same anthracycline as given induction, as consolidation.⁵² There was no difference in CR rate, induction mortality rate, DFS, or OS among the three induction arms. Therefore, there is no evidence that one anthracycline is better than another for induction in older

adults. In younger adults, emerging data suggest the same conclusion.

Randomized Trials of Cytarabine Dose in Induction Therapy

Cytarabine is one of the most active single drugs for the treatment of AML. Increased doses of cytarabine in induction have been explored. In a prospective randomized trial conducted at a single institution,⁵³ intermediate-dose cytarabine at 500 mg/m² given with daunorubicin at 60 mg/m² provided similar results to conventional-dose cytarabine at 200 mg/m² with respect to CR rates (74% in the intermediate-dose arm and 71% in the conventional-dose arm) and DFS. Patients receiving the higher dose of cytarabine had a higher CR rate after one course of induction, but this was not statistically significant.

A number of studies have shown that HiDAC is effective treatment for patients with relapsed and refractory leukemia. Therefore, several trials have tested the benefits of HiDAC in induction (Table 4). Two prospective randomized trials that

accrued relatively large numbers of patients compared HiDAC with standard induction while employing the same postremission therapy in both arms. The Australian Leukemia Study Group (ALSG)⁵⁴ compared g/m² of HiDAC every 12 hours for 8 days on alternate days plus 50 mg/m² of daunorubicin and 75 mg/m² of etoposide to conventional induction with etoposide. The Southwest Oncology Group (SWOG)⁵⁵ compared 2 g/m² of cytarabine every 12 hours for 6 days plus daunorubicin at 45 mg/m² to conventional induction. Both trials failed to identify a higher CR rate with HiDAC compared with standard induction, but the high-dose regimen was associated with increased hematologic and extramedullary toxicity, including nausea, emesis, and ophthalmologic toxicity. In one of these studies, patients randomized to HiDAC had increased cerebellar toxicity. Both studies showed a longer DFS (but not OS) among patients receiving the high-dose regimen. However, these studies do not provide information as to whether HiDAC must be given in induction or if it would yield similar outcome results if given as consolidation.

Randomized Trials of Additional Drugs During Induction Therapy

The ALSG compared standard-dose cytarabine plus daunorubicin (7 + 3) to 7 + 3 plus etoposide at 75 mg/m² per day for 7 days (7 + 3 + 7) followed by consolidation with the same agents over a shorter time, 5 + 2 vs 5 + 2 + 5.⁵⁶ Patients then received maintenance with cytarabine and 6-thioguanine for 2 years. Although there was a significantly longer DFS on the etoposide arm, OS was not improved. Updated results reveal that the median OS was not significantly improved on 7 + 3 + 7 compared with 7 + 3 (13 months vs 9 months, $P=0.24$).⁵⁷ The 5- and 10-year OS rates for 7 + 3 + 7 were 19% and 16%, respectively, compared with 16% and 12%, respectively, for 7 + 3. However, the OS among patients less than 55 years of age was significantly longer on the 7 + 3 + 7 arm ($P=0.04$) with 5- and 10-year OS rates of 25% and 25%, respectively, and 17% and 14%, respectively for 7 + 3. Older patients experienced significantly more toxicity and no benefit in outcome. Therefore, in younger patients, intensified induction may improve CR duration and OS without necessarily improving the CR rate. However, caution in interpretation is required, given that there was no stratification at randomization based on age.

Updated results of the HiDAC + 3 + 7 vs 7 + 3 + 7 trial conducted by the ALSG⁵⁷ show that the median remission duration was 46 months for HiDAC + 3 + 7 and 12

months for 7 + 3 + 7 ($P=0.0007$). The DFS rate among patients achieving CR at 5 years was 48% on the HiDAC arm compared with 25% on the 7 + 3 + 7 arm, and there were no relapses on either arm beyond 54 months. The difference in OS between the two arms approached statistical significance ($P=0.053$). These data suggest that intensified induction, as administered here, may improve outcome.

The MRC in the United Kingdom evaluated the benefits of adding etoposide to an induction regimen of anthracycline and cytarabine in the AML-10 trial.⁵⁸ More than 1,800 patients 55 years of age and younger were randomized to either 7 + 3 (daunorubicin at 50 mg/m²) + 6-thioguanine for two courses, the first with cytarabine and 6-thioguanine given for 10 days and the second with both agents given for 8 days, or 7 + 3 (daunorubicin at 50 mg/m²) plus 100 mg/m² of etoposide per day for 5 days for two courses, the first with cytarabine given for 10 days and the second with cytarabine given for 8 days. Patients achieving CR received two cycles of consolidation. Induction mortality was somewhat higher on the etoposide arm (9% vs 6%, $P=0.06$). The CR rates between the two arms did not differ. There were no differences in either DFS rate (42% at 6 years for 7 + 3 and 43% for 7 + 3 + 5) or OS rate (40% for both groups). This trial further suggests that the addition of etoposide to standard anthracycline-cytarabine induction is not helpful, although the results may be difficult to interpret because of the potential contribu-

tion of 6-thioguanine. Therefore, there is level II, grade C evidence that the addition of etoposide during induction is not beneficial.

Sequential Standard-Dose Cytarabine Followed by High-Dose Cytarabine in Induction Therapy

Induction can also be intensified by adding HiDAC during the 3 days immediately following standard cytarabine plus daunorubicin induction. Mitus and colleagues⁵⁹ administered HiDAC on days 8, 9, and 10 of induction to exploit potential recruitment into the cell cycle and to avoid administering an entire second cycle of induction for patients with residual leukemia after a first cycle. CR was achieved in 89% of patients, and essentially all patients achieved CR after one cycle of chemotherapy. Both ECOG and SWOG have completed phase II studies^{60,61} testing this strategy. No difference was observed in the CR rate among patients given the intensified induction compared to historical results with standard induction in either trial. The German AML Cooperative Group⁶² randomized newly diagnosed patients to either two courses of standard-dose cytarabine with daunorubicin and 6-thioguanine or one course of the same chemotherapy followed by HiDAC with mitoxantrone on day 21 regardless of the marrow findings. There were no differences in the CR rates (65% in the standard-dose vs 71% on the HiDAC arm, $P=ns$), in the induction death rate (18% vs 14%, $P=ns$), or in the relapse-free survival at 5 years (29%

vs 35%, $P=ns$). However, high-risk patients (ie, more than 40% residual blasts on D16 marrow, unfavorable karyotype, and elevated LDH) had a higher CR rate (65% vs 49%, $P=0.004$), a superior event-free survival rate at 5 years (17% vs 12%, $P=.012$), and a median OS at 5 years (13 months vs 8 months, $P=0.009$).

Hematopoietic Growth Factors During Induction Therapy

Hematopoietic growth factors have been shown to shorten the period of neutropenia after induction therapy in AML (Table 5). Many prospective randomized trials have been conducted, but they vary with respect to design, patient age, and induction regimen.⁶³⁻⁷⁴ In the ECOG trial, patients between

ages 55 and 70 received daunorubicin at 60 mg/m² plus cytarabine at 100 mg/m² for 7 days. The CR rate was better in the GM-CSF arm (60%) compared with the placebo arm (44%) ($P=.08$) and median times were significantly shorter on the GM-CSF arm.⁶⁴ Furthermore, infectious toxicity was significantly reduced on the GM-CSF arm ($P=.015$). In an intent-to-treat analysis considering all randomized patients, the median survival was significantly longer for patients receiving GM-CSF (10.6 months vs 4.8 months). This difference was attributable to increased early mortality in the placebo group. The design of the CALGB trial reported by Stone and colleagues⁶⁸ differed from the ECOG trial in that patients received GM-CSF or placebo on

day 8 (vs day 11 in the ECOG study) immediately after completion of induction therapy, regardless of whether marrow aplasia was present. Due to perceived toxicity, 30% of patients discontinued the study drug in either arm. There was no difference in CR rates among patients assigned to GM-CSF vs placebo (51% vs 54%, $P=0.61$). No differences were seen between the two groups in the incidence of both severe and lethal infection and the incidence of regrowth of leukemia. The median duration of neutropenia was only minimally shorter among patients receiving GM-CSF (15 days vs 17 days, $P=0.02$). All studies demonstrated a shorter period of myelosuppression. In a study conducted in France,⁶⁵ CR increased but survival was not prolonged. Neither

Table 5. — Randomized Trials of Growth Factors After Induction Therapy in AML

Author	Number of Patients	Growth Factor	Start Day	Marrow Aplasia	Growth Factor vs Control	
					CR (%)	Median Days ANC to 1000/ μ L
Rowe ⁶⁴	117	GM-CSF	11	Yes	60 vs 44	12 vs 18*
Dombret ⁶⁵	173	G-CSF	8	No	63 vs 32*	21 vs 27*
Heil ⁶⁶	521	G-CSF	8	No	69 vs 68	5 days**
Godwin ⁶⁷	234	G-CSF	11	Yes	42 vs 49	3-4 days**
Stone ⁶⁸	379	GM-CSF	8	No	52 vs 54	15 vs 17*
Zittoun ⁶⁹	53	GM-CSF	8	No	48 vs 77*	Not different
Löwenberg ⁷⁰	316	GM-CSF	1-8	No	56 vs 55*	26 vs 31*
Link ⁷¹	187	G-CSF	9	No	60 vs 43*	12 vs 18*
Goldstone ⁷²	800	G-CSF	8	No	72 vs 75	15 vs 20
Witz ⁷³	209	GM-CSF	1	No	63 vs 61	22 vs 26*

* $P \leq 0.05$
 ** Recovery was faster with G-CSF by 3-5 days. Dates not stated.
 CR = complete remission
 ANC = absolute neutrophil count
 From Rowe JM, Liesveld JL. Hematopoietic growth factors in acute leukemia. *Leukemia*. 1997;11:328-341. Adapted with permission.

the CALGB study nor the SWOG study showed that a shorter period of myelosuppression resulted in improvement in either the CR rate or OS. There is level I, grade A evidence from 10 prospective randomized trials that hematopoietic growth factors do shorten the period of neutropenia following induction chemotherapy but with little evidence of a significant improvement in outcome.

In the aggregate experience, these studies suggest that growth factors shorten the period of neutropenia following induction chemotherapy and, in several studies, significantly reduce morbidity. However, the CR rate and OS are generally not improved. Therefore, growth factors appear safe with little or no risk of leukemic cell stimulation.

Postremission Therapy

A variety of approaches have been explored to prevent relapse. Such strategies have included low-dose maintenance therapy, intensive consolidation therapy, or high-dose chemotherapy or chemoradiotherapy, with either allogeneic or autologous bone marrow or stem cell transplantation.

Maintenance Therapy

A prospective randomized trial⁷⁵ conducted by ECOG suggested that maintenance therapy with 6-thioguanine plus cytarabine at 60 mg/m² once a week for 2 years offered a benefit in remis-

sion duration compared with no maintenance treatment (median remission duration of 8.1 vs 4.1 month, $P=0.003$), although no significant survival difference was identified. In another prospective randomized ECOG trial,⁷⁶ repeated courses of low-dose cytarabine were compared to observation as maintenance therapy after induction of a second CR in patients with relapsed or refractory AML (Fig 2). The median DFS among 41 patients assigned to low-dose cytarabine was 7.4 months compared to 3.3 months for the 45 patients receiving no additional treatment ($P=0.084$). However, the OS among the two groups was not different (10.9 months vs 7.0 months, $P=0.615$). Buchner and colleagues⁷⁷ recently analyzed

long-term follow-up data and observed a benefit to monthly maintenance for 3 years (5-year DFS rate of 23% vs 6%). In an EORTC-HOVON trial, 76 patients aged 61 years or more achieving CR were randomized to no further therapy and 75 patients to eight cycles of low-dose cytarabine (10 mg/m² subcutaneously) every 12 hours for 12 days every 6 weeks following consolidation with the same agents used in induction.⁷⁰ An advantage in DFS was observed among patients receiving maintenance low-dose cytarabine every 6 weeks for 1 year (median DFS rate was 20% vs 7% and 5-year DFS rate was 13% vs 7%, $P=0.006$). However, OS was not different (5-year OS rate was 18% vs 15%, $P=0.29$). The AML-9 study⁷⁸ conducted by the

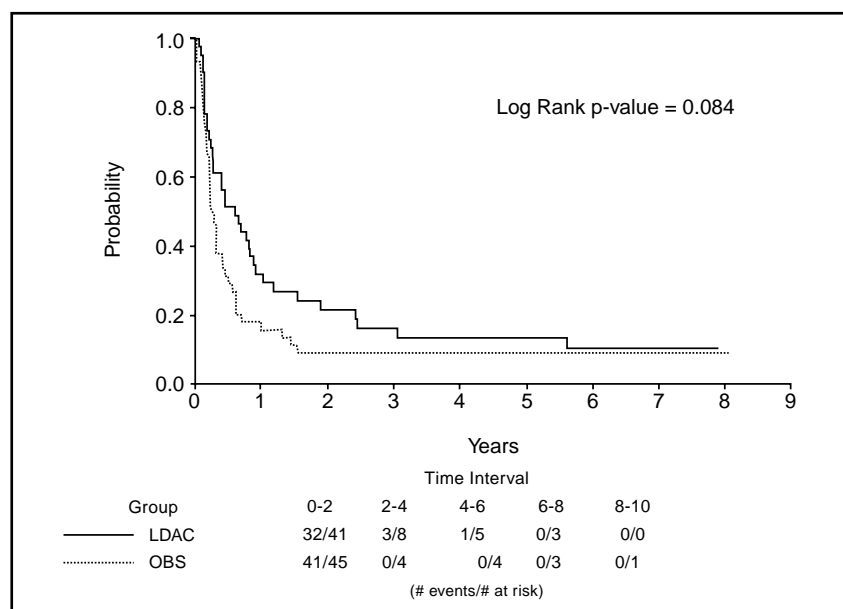


Fig 2. — Kaplan-Meier estimate for leukemia-free survival for patients with relapsed or refractory AML who achieved a second remission then were randomized to either low-dose cytarabine maintenance therapy or no additional therapy. From Robles C, Kim KM, Oken MM, et al. Low-dose cytarabine maintenance therapy vs observation after remission induction in advanced acute myeloid leukemia: an Eastern Cooperative Oncology Group Trial (E5483). *Leukemia*. 2000;14:1349-1353. Reprinted with permission.

MRC in the United Kingdom randomized patients in CR to maintenance treatment for 1 year with 8 courses of cytarabine at 70 mg/m² given subcutaneously every 12 hours and 6-thioguanine at 100 mg/m² given orally every 12 hours for 5 days per month followed by four courses of cyclophosphamide, vincristine, cytarabine, and prednisone (COAP) or observation. With this therapy, relapse was delayed but not prevented, with no improvement in the OS at 5 years. Therefore, contemporary studies employing various maintenance regimens consistently show a benefit in DFS but not OS (level 1, grade B evidence).

Intensive Consolidation Chemotherapy

Phase II nonrandomized studies and retrospective analyses of cooperative group studies have suggested that increasing the intensity of postremission therapy is beneficial.^{5,6,79} Several studies have prospectively evaluated the role of intensive postremission consolidation with HiDAC. The CALGB randomly assigned 596 patients in CR to receive four courses of cytarabine at one of three doses: 100 mg/m² per day by continuous IV infusion for 5 days; 400 mg/m² per day by continuous IV infusion for 5 days; and 3 g/m² as a 3-hour IV infusion twice daily on days 1, 3, and 5 (Fig 3).⁷⁹ High rates of central nervous system toxicity were observed in patients older than 60 years of age randomized to the high-dose regimen. Randomization was subsequently

limited to patients 60 years of age or younger. The DFS rate was 21% in the 100-mg arm, 25% in the 400-mg arm, and 39% in the 3-g arm. The results were most significant in patients with favorable cytogenetics. This trial demonstrated a dose-response effect for cytarabine in patients undergoing postremission therapy. Although the HiDAC regimen used in this trial has become widely adopted, it should be noted that after the four courses of cytarabine, all patients received 4 monthly cycles of cytarabine at 100 mg/m² every 12 hours for 5 days by subcutaneous injection and daunorubicin at 45 mg/m² IV infusion on day 1. Remissions achieved in this trial were durable, with few relapses after 20 months. In an ECOG trial,⁸⁰ patients without HLA-matched siblings were randomized to 2 years of continuous out-

patient maintenance therapy with cytarabine and 6-thioguanine or a single course of intensive consolidation with cytarabine at 3 g/m² IV every 12 hours for 12 doses followed by 100 mg/m² of amsacrine per day IV for 3 days.⁸⁰ The 4-year event-free survival rate was 27% for the intensive consolidation arm and 16% for the maintenance arm ($P=0.068$). This difference was statistically significant in patients younger than 60 years of age. The number of HiDAC courses required for optimal postremission therapy is uncertain.

The Finnish Leukemia Group⁸¹ randomized patients less than 65 years of age in CR after two courses of induction to either four additional consolidation courses after two courses of HiDAC-containing consolidation or to observation. No benefit was observed for

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patients randomized to the longer consolidation program, suggesting early intensive consolidation is likely the most important influence on outcome rather than the number of cycles of intensive chemotherapy.

Prospective Studies of Intensive Postremission Chemotherapy, AlloBMT, and AutoBMT

Several studies have compared prospectively the benefits of intensive consolidation with HiDAC, autologous bone marrow (or stem cell) transplantation, and allogeneic HLA-matched bone marrow transplantation (BMT). Autologous stem cell transplantation involves the administration of higher chemotherapy doses, but it is limited by the lack of the graft-vs-leukemia effect associated with allogeneic transplantation. Furthermore, there is a theoretic risk of infusion of occult residual leukemic cells. Allogeneic transplantation provides the best antileukemic potential, but it is consistently associated with a higher risk of treatment-related mortality

than the other two strategies. All of these studies have assigned younger patients with an HLA-matched donor to allogeneic transplantation and randomized other patients to either consolidation chemotherapy or autologous transplantation or between the latter two strategies (Table 6).⁸²⁻⁸⁵ The earliest study carried out as a collaboration between the EORTC and GIMEMA included patients with a CR: 168 patients in first CR were assigned to allogeneic transplantation, and 254 were randomly assigned to one of the other two groups — 126 were randomized to a second cycle of consolidation with cytarabine at 2 g/m² every 12 hours on days 1-4 plus daunorubicin at 45 mg/m² on days 5-7, and 128 patients were randomized to autologous transplantation with cyclophosphamide/total body irradiation (TBI) or busulfan/TBI (55% of patients) as the preparative regimen.⁸² Only 74% of patients randomized to autologous transplantation actually completed the treatment because of early relapse and toxicity. Nevertheless, the DFS rate at 4 years, by an intent-to-treat analysis, was approximately 50%. This

outcome is similar to that achieved among patients undergoing allogeneic transplantation (cyclophosphamide/TBI in approximately 66% of patients as the preparative regimen and busulfan/cyclophosphamide in 34%) who had a DFS of 55% rate at 4 years. These results were significantly better than those observed among patients receiving consolidation (30%). However, the OS at 4 years for all three treatment groups was similar (59% allogeneic, 56% autologous, and 46% consolidation). While relapse was more frequent among patients randomized to autologous transplantation, treatment-related mortality was higher among those assigned allogeneic transplantation.

Despite a similar trial design (although the autologous transplants were carried out with purged bone marrow), different observations were made in the trial conducted by ECOG, SWOG, and CALGB.⁸³ The DFS rate associated with allogeneic transplantation was not significantly longer (43% at 4 years) than that associated with autologous transplantation (34%) or consolidation with HiDAC (34%). However, OS following HiDAC was longer than that after autologous or allogeneic transplantation. The discrepancy between DFS and OS likely relates to the opportunity to undergo transplantation at relapse among patients initially assigned consolidation chemotherapy.

In a study by Harousseau et al,⁸⁴ there was no difference in the 4-year DFS or OS between patients randomized to autologous transplantation and those randomized to

Table 6. — Prospective Randomized Trials of Consolidation Chemotherapy vs BMT in AML

Author	4-Year DFS/OS (%)		
	Consolidation Chemotherapy	Autologous BMT	Assigned Allogeneic BMT
Zittoun ⁸²	30/46	48/56	55/59
Cassileth ⁸³	34/52	34/43	43/46
Harousseau ⁸⁴	43/59 [3]	48/52 [6.5]	49/55 [22]
Burnett ⁸⁵	40/57*	54/45 [12]	-
* 7 years			

consolidation. The trial conducted by the MRC was unique because it demonstrated that the addition of autologous transplantation following three cycles of consolidation (two similar to induction and one including cytarabine at 1 g/m² every 12 hours for 3 days) reduced the risk of relapse and a statistical effect was seen on OS.⁶⁵

The interpretations of these studies require caution. First, in all studies, a significant number of patients randomized to autologous transplantation do not receive the assigned treatment. Second, allogeneic transplantation offers the potential for graft-vs-leukemia effect and is associated with the lowest risk of relapse. However, higher treatment-related mortality compared with autologous transplantation and consolidation chemotherapy diminishes the impact of the greater antileukemic potential and thus a benefit in OS is not observed. Third, it is likely that the mortality rate associated with both autologous and allogeneic transplantation will continue to decrease as the techniques of transplantation improve, such as the introduction of autologous peripheral blood stem cell transplantation and improvements in T-cell depletion techniques for allogeneic transplantation.^{86,87} Furthermore, recent studies suggest that the outcome for allogeneic transplantation in patients older than age 40 may not be worse than for younger patients.⁸⁸ There are improvements in all three postremission strategies that require frequent reappraisal of the benefits and hazards of each approach.^{72,89}

Treatment for Acute Promyelocytic Leukemia

Acute promyelocytic leukemia (APL) is treated differently from all other subtypes of AML and has become the most curable subtype of AML in adults. Phase II trials have confirmed the effectiveness of the vitamin A derivative all-trans retinoic acid (ATRA) as differentiation therapy in patients with APL.⁹⁰⁻⁹⁹ Two prospective randomized trials have compared ATRA with or without chemotherapy to chemotherapy alone for induction.¹⁰⁰⁻¹⁰¹ Following CR, patients in both trials received two cycles of consolidation (7 + 3 followed by intermediate-dose cytarabine plus daunorubicin in the APL-91 trial¹⁰⁰ and 7 + 3 followed by HiDAC plus daunorubicin in the North American Intergroup trial¹⁰¹). In the latter trial, patients in CR after two cycles of consolidation were randomized either to either 1 year of daily maintenance with ATRA or to observation. In both trials, the CR rates on both arms were not statistically different. However, event-free survival, DFS, and OS were markedly improved with ATRA such that approximately 70% of patients remain disease-free at 4 years. This benefit was attributable to a decrease in the relapse rate with ATRA. In the North American Intergroup trial, patients induced with standard induction chemotherapy and maintained with ATRA had an outcome identical to patients who received ATRA during induction. The most serious and life-threatening complication of differentiation therapy with ATRA is the retinoic acid syndrome, a cardiorespiratory

distress syndrome manifested by interstitial pulmonary infiltrates, pleural or pericardial effusions, hypoxemia, and episodic hypotension with otherwise unexplained weight gain.^{102,103} The syndrome may be related to the rapid development of hyperleukocytosis, which can be observed with ATRA induction. The syndrome usually resolves quickly if corticosteroids (10 mg of dexamethasone b.i.d. for at least 3 days) are administered at the earliest sign or symptom. The APL-93 trial showed that administering concurrent ATRA plus chemotherapy reduces the relapse rate compared to sequential ATRA for induction followed by chemotherapy.¹⁰⁴ This was observed even among patients presenting with a relatively low white blood cell count. Therefore, the standard induction strategy for APL now includes ATRA plus chemotherapy for all patients.

The MRC randomized patients either to a 5-day short course of ATRA (to reduce the coagulopathy but avoid the retinoic acid syndrome) before commencing chemotherapy or to concomitant ATRA and chemotherapy until initial CR.¹⁰⁵ The latter strategy was associated with an improved outcome. Although the best chemotherapy regimen to include in induction is not established, anthracycline alone during induction is sufficient.^{97,99} The best consolidation regimen has not been established; however, it appears that all patients should receive at least two cycles of consolidation with either anthracycline plus cytarabine (as in the APL-91 trial), anthracycline plus

cytarabine followed by HIDAC (as in the North American Intergroup Trial), or intermediate-dose cytarabine plus idarubicin followed by mitoxantrone, etoposide, cytarabine, and 6-thioguanine (as in the GIMEMA trial). Anthracyclines alone as consolidation may well be sufficient.^{99,106} The precise role of maintenance therapy with ATRA continues to evolve. The North American Intergroup Trial and the APL-93 trial both suggest a beneficial role.

Treatment of Older Adults

The treatment of older adults with AML is problematic, and the results are disappointing.^{4,6} Older patients do not tolerate intensive chemotherapy as well as younger patients.^{107,108} In addition, older adults with AML frequently have leukemic cells with poor prognosis karyotypes.¹⁰⁹ Finally, such patients have leukemic cells that frequently express the MDR marker P-glycoprotein, which renders their cells more resistant to chemotherapy than the cells of younger patients.¹¹⁰

An EORTC trial¹¹¹ randomized patients older than 65 years of age either to immediate intensive induction chemotherapy or to supportive care with the introduction of mild cytoreductive chemotherapy for relief of leukemia-related symptoms. An improved survival was noted for patients receiving initial intensive chemotherapy (21 weeks vs 11 weeks, $P=.015$). Some investigators have recommended

low-dose cytarabine as a putative differentiating agent since this approach is less toxic and may induce CR in up to 50% of patients, as reported in a small series.¹¹² However, the drug likely acts as a cytotoxic agent,¹¹³ and this treatment is associated with significant morbidity and mortality.¹¹⁴ Most series report CR rates of 15%-23%.¹¹⁵⁻¹¹⁷ Stasi and colleagues¹⁶ reported that among 92 patients age 60 or older suitable for aggressive chemotherapy, the CR rate was 52%. The median CR duration was 35 weeks and event-free survival was 27 weeks. In their multivariate analysis, the three risk factors predictive of a longer event-free survival were abnormal karyotype, CD14 expression on leukemic cells, and age older than 67 years. Bow and co-investigators¹¹⁸ evaluated a combination of mitoxantrone and etoposide as remission induction in older adults. A CR rate of 55% was achieved with an induction mortality rate of 12%.

Primary Therapy of AML for Patients Outside of Clinical Trials

For patients 55 years of age or less, standard induction includes either daunorubicin or idarubicin and cytarabine. Hematopoietic growth factors may be administered safely following induction. If an HLA-compatible sibling is available, allogeneic BMT can be considered, either immediately after induction or after a single cycle of intensive postremission therapy that may include cytarabine at 3 g/m² every 12 hours for 6 days or 3

g/m² twice daily on days 1, 3, and 5. In an International Bone Marrow Transplant Registry analysis, no benefit in outcome after HLA-matched sibling transplantation was observed for any dose of consolidation chemotherapy following successful remission induction.¹¹⁹ If no HLA-compatible sibling is available, postremission therapy is given either with one cycle of cytarabine, as above, with an autologous stem cell transplant using peripheral blood derived stem cells or with four cycles of cytarabine if an autologous stem cell transplant is not to be carried out.

For patients over 55-65 years of age, induction with either daunorubicin and idarubicin or mitoxantrone and cytarabine is given followed by consolidation with cytarabine at 1.5 g/m² every 12 hours for 6 days for 1-2 cycles. Autologous stem cell transplantation may be considered if concurrent medical problems do not preclude such an approach. For patients older than 69 years of age, the dose of postremission cytarabine may be reduced to 1.5 g/m² for 6 doses. Maintenance therapy with low-dose cytarabine may be valuable.

Specific karyotype abnormalities, as well as other risk factors including age and comorbid illness, may influence the therapeutic decisions. For example, patients with favorable karyotypes may fare particularly well with intensive consolidation or transplant.^{89,120-122} The outcome of patients with unfavorable karyotypes is poor with intensive cytarabine consolidation. There-

fore, allogeneic transplantation should be considered. Improvements in both consolidation chemotherapy and stem cell transplantation will require frequent re-evaluation to identify the best strategy for postremission therapy for a given patient population.

Patients with newly diagnosed APL should be treated with ATRA and concurrent chemotherapy. The best chemotherapy to administer in induction has not been established but may include only an anthracycline, either daunorubicin or idarubicin. Higher doses, such as daunorubicin at doses of at least 50-60 mg/m² per day for 3 days, can be considered. Once CR is achieved, ATRA can be discontinued, and 2-3 cycles of anthracycline-rich consolidation chemotherapy are administered. An anthracycline alone may be sufficient. The role of ATRA during consolidation remains to be determined. Molecular studies are carried out at the end of consolidation and then serially in order to detect early relapse. Maintenance therapy, either with ATRA or with ATRA plus low-dose chemotherapy with 6-mercaptopurine and methotrexate, appears to be beneficial in preventing relapse.

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References

1. Rai KR, Holland JF, Glidewell OJ, et al. Treatment of acute myelocytic leukemia: a study by Cancer and Leukemia Group B. *Blood*. 1981;58:1203-1212.
2. Yates J, Glidewell O, Wiernik P, et al. Cytosine arabinoside with daunorubicin or adriamycin for therapy of acute myelocytic leukemia: a CALGB study. *Blood*. 1982; 60:454-462.
3. Preisler HD, Anderson K, Rai K, et al. The frequency of long-term remission in patients with acute myelogenous leukaemia treated with conventional maintenance chemotherapy: a study of 760 patients with a minimum follow-up time of 6 years. *Br J Haematol*. 1989;71:189-194.
4. Bandini G, Zuffa E, Rosti G, et al. Long-term outcome of adults with acute myelogenous leukemia: results of a prospective randomized study of chemotherapy with a minimal follow-up of 7 years. *Br J Haematol*. 1991;77:486-490.
5. Rowe JM, Andersen J, Cassileth PA, et al. Clinical trials of adults with acute myelogenous leukemia: experience of the Eastern Cooperative Oncology Group. In: Hiddemann W, Buchner T, Wormann B, et al, eds. *Acute Leukemia IV: Experimental Approaches and Novel Therapies*. Berlin: Springer-Verlag; 1994:542.
6. Bennett JM, Young ML, Andersen JW, et al. Long-term survival in acute myeloid leukemia: the Eastern Cooperative Oncology Group experience. *Cancer*. 1997;80(11 suppl):2205-2209.
7. Bennett JM, Catovsky D, Daniel MT, et al. Proposed revised criteria for the classification of acute myeloid leukemia: a report from the French-American-British Cooperative Group. *Ann Intern Med*. 1985;103:620-625.
8. Harris NL, Jaffe ES, Diebold J, et al. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting. Airlie House, Virginia, November 1997. *J Clin Oncol*. 1999;17:3835-3849.
9. Keating MJ, Smith TL, Kantarjian H, et al. Cytogenetic pattern in acute myelogenous leukemia: a major reproducible determinant of outcome. *Leukemia*. 1988;2:403-412.
10. Van Putten WLJ, Löwenberg B. Prognostic factors in adult AML. *Blood*. 1997; 90:65a. Abstract.
11. Fenaux P, Preudhomme C, Lai JL, et al. Cytogenetics and their prognostic value in de novo acute myeloid leukaemia: a report on 283 cases. *Br J Haematol*. 1989; 73:61-67.
12. Schiffer CA, Lee EJ, Tomiyasu T, et al. Prognostic impact of cytogenetic abnormalities in patients with de novo acute nonlymphocytic leukemia. *Blood*. 1989;73:263-270.
13. Dastugue N, Payen C, Lafage-Pochitaloff M, et al. Prognostic significance of karyotype in de novo adult acute myeloid leukemia: the BGMT group. *Leukemia*. 1995;9:1491-1498.
14. van den Heuvel-Eibrink MM, van der Holt B, te Boekhorst PA, et al. MDR1 expression is an independent prognostic factor for response and survival in de novo acute myeloid leukaemia. *Br J Haematol*. 1997; 99:76-83.
15. Leith CP, Kopecky KJ, Godwin J, et al. Acute myeloid leukemia in the elderly: assessment of multidrug resistance (MDR1) and cytogenetics distinguishes biologic subgroups with remarkably distinct responses to standard chemotherapy. A Southwest Oncology Group study. *Blood*. 1997;89: 3323-3329.
16. Stasi R, Venditti A, Del Poeta G, et al. Intensive treatment of patients age 60 years and older with de novo acute myeloid leukemia: analysis of prognostic factors. *Cancer*. 1996;77:2476-2488.
17. Grimwade D, Walker H, Oliver F, et al. The importance of diagnostic cytogenetics on outcome in AML: analysis of 1,612 patients entered into the MRC AML 10 trial. The Medical Research Council Adult and Children's Leukemia Working Parties. *Blood*. 1998;92:2322-2333.
18. Mrozek K, Heinonen K, de la Chapelle A, et al. Clinical significance of cytogenetics in acute myeloid leukemia. *Semin Oncol*. 1997;24:17-31. Review.
19. Schoch C, Haase D, Haferlach T, et al. Fifty-one patients with acute myeloid leukemia and translocation t(8;21)(q22;q22): an additional deletion in 9q is an adverse prognostic factor. *Leukemia*. 1996; 10:1288-1295.
20. Schoch C, Haase D, Fonatsch C, et al. The significance of trisomy 8 in de novo acute myeloid leukemia: the accompanying chromosome aberrations determine the prognosis. *Br J Haematol*. 1997;99:605-611.
21. Yamamoto K, Seto M, Iida S, et al. A reverse transcriptase-polymerase chain reaction detects heterogeneous chimeric mRNAs in leukemias with 11q23 abnormalities. *Blood*. 1994;83:2912-2921.
22. Mrozek K, Heinonen K, Lawrence D, et al. Adult patients with de novo acute myeloid leukemia and t(9;11)(p22;q23) have a superior outcome to patients with other translocations involving band 11q23: a Cancer and Leukemia Group study. *Blood*. 1997;90:4532-4538.
23. Archimbaud E, Charrin C, Magaud JP, et al. Clinical and biological characteristics of adult de novo and secondary acute

myeloid leukemia with balanced 11q23 chromosomal anomaly or MLL gene rearrangement compared to cases with unbalanced 11q23 anomaly: confirmation of the existence of different entities with 11q23 breakpoint. *Leukemia*. 1998;12:25-33.

24. Baer MR, Stewart CC, Lawrence D, et al. Expression of the neural cell adhesion molecule CD56 is associated with short remission duration and survival in acute myeloid leukemia with t(8;21)(q22;q22). *Blood*. 1997;90:1643-1648.

25. Baudard M, Beauchamp-Nicoud A, Delmer A, et al. Has the prognosis of adult patients with acute myeloid leukemia improved over years? A single institution experience of 784 consecutive patients over a 16-year period. *Leukemia*. 1999;13:1481-1490.

26. Freireich EJ. Arabinosyl cytosine: a 20-year update. *J Clin Oncol*. 1987;5:523-524.

27. Coltman CA Jr, Freireich EJ, Pendleton O, et al. Adult acute leukemia studies utilizing cytarabine: early Southwest Oncology Group trials. *Med Pediatr Oncol*. 1982;10:173-183.

28. Weil M, Glidewell OJ, Jacquillat C, et al. Daunorubicin in the therapy of acute granulocytic leukemia. *Cancer Res*. 1973;33:921-928.

29. Preisler H, Davis RB, Kirshner J, et al. Comparison of three remission induction regimens and two postinduction strategies for the treatment of acute nonlymphocytic leukemia: a Cancer and Leukemia Group B study. *Blood*. 1987;69:1441-1449.

30. Dillman RO, Davis RB, Green MR, et al. A comparative study of two different doses of cytarabine for acute myeloid leukemia: a phase III trial of Cancer and Leukemia Group B. *Blood*. 1991;78:2520-2526.

31. Rowe JM, Tallman MS. Intensifying induction therapy in acute myeloid leukemia: has a new standard of care emerged? *Blood*. 1997;90:2121-2126.

32. Speth PA, Minderman H, Haanen C. Idarubicin vs daunorubicin: preclinical and clinical pharmacokinetic studies. *Semin Oncol*. 1989;16:2-9. Review.

33. Curtis JE, Minden MD, Minkin S, et al. Sensitivities of AML blast stem cells to idarubicin and daunorubicin: a comparison with normal hematopoietic progenitors. *Leukemia*. 1995;9:396-404.

34. Ross D, Tang Y, Comblatt B. Idarubicin (IDA) in less vulnerable to transport-mediated multidrug resistance (MDR) than its metabolite idarubicinol (IDA-ol) or daunorubicin. *Blood*. 1993;10:1015.

35. Roovers DJ, van Vliet M, Bloem AC, et

al. Idarubicin overcomes P-glycoprotein-related multidrug resistance: comparison with doxorubicin and daunorubicin in human multiple myeloma cell lines. *Leuk Res*. 1999;23:539-548.

36. Berman E, Heller G, Santorsa J, et al. Results of a randomized trial comparing idarubicin and cytosine arabinoside with daunorubicin and cytosine arabinoside in adult patients with newly diagnosed acute myelogenous leukemia. *Blood*. 1991;77:1666-1674.

37. Wiernik PH, Banks PL, Case DC Jr, et al. Cytarabine plus idarubicin or daunorubicin as induction and consolidation therapy for previously untreated adult patients with acute myeloid leukemia. *Blood*. 1992;79:313-319.

38. Vogler WR, Velez-Garcia E, Weiner RS, et al. A phase III trial comparing idarubicin and daunorubicin in combination with cytarabine in acute myelogenous leukemia: a Southeastern Cancer Study Group study. *J Clin Oncol*. 1992;10:1103-1111.

39. Mandelli F, Petti MC, Ardia A, et al. A randomised clinical trial comparing idarubicin and cytarabine to daunorubicin and cytarabine in the treatment of acute nonlymphoid leukaemia: a multicentric study from the Italian Cooperative Group GIMEMA. *Eur J Cancer*. 1991;27:750-755.

40. The AML Collaborative Group. A systematic collaborative overview of randomized trials comparing idarubicin with daunorubicin (or other anthracyclines) as induction therapy for acute myeloid leukaemia. *Br J Haematol*. 1998;103:100-109.

41. Grant S, Arlin Z, Gewirtz D, et al. Effect of pharmacologically relevant concentrations of mitoxantrone or the in vitro growth of leukemic blast progenitors. *Leukemia*. 1991;5:336-339.

42. Arlin Z, Case DC Jr, Moore J, et al. Randomized multicenter trial of cytosine arabinoside with mitoxantrone or daunorubicin in previously untreated adult patients with acute nonlymphocytic leukemia (ANLL) Lederle Cooperative Group. *Leukemia*. 1990;4:177-183.

43. Wahlin A, Hornsten P, Hedenus M, et al. Mitoxantrone and cytarabine versus daunorubicin and cytarabine in previously untreated patients with acute myeloid leukemia. *Cancer Chemother Pharmacol*. 1991;28:480-483.

44. Pavlovsky S, Gonzalez Llaven J, Garcia Martinez MA, et al. A randomized study of mitoxantrone plus cytarabine versus daunorubicin plus cytarabine in the treatment of previously untreated adult patients with acute nonlymphocytic leukemia. *Ann Hematol*. 1994;69:11-15.

45. Hansen OP, Pedersen-Bjergaard J, Ellegaard J, et al. Aclarubicin plus cytosine arabinoside versus daunorubicin plus cytosine arabinoside in previously untreated patients with acute myeloid leukemia: a Danish national phase III trial. The Danish Society of Hematology Study Group on AML, Denmark. *Leukemia*. 1991;5:510-516.

46. Berman E, Arlin ZA, Gaynor J, et al. Comparative trial of cytarabine and thioguanine in combination with amsacrine or daunorubicin in patients with untreated acute nonlymphocytic leukemia: results of the L-16M protocol. *Leukemia*. 1989;3:115-121.

47. Buchner T, Hiddemann W, Wormann B, et al. Daunorubicin 60 instead of 30 mg/sqm improves response and survival in elderly patients with AML. *Blood*. 1997;90:2596. Abstract.

48. Feldman EJ, Seiter K, Damon L, et al. A randomized trial of high- vs standard-dose mitoxantrone with cytarabine in elderly patients with acute myeloid leukemia. *Leukemia*. 1997;11:485-489.

49. Rowe JM, Neuberger D, Friedenbergs W, et al. A Phase III study of daunorubicin vs idarubicin vs mitoxantrone for older adult patients (>55 years) with acute myelogenous leukemia (AML): a study of the Eastern Cooperative Oncology Group (E3993). *Blood*. 1998;92:1284.

50. Löwenberg B, Suciú S, Archimbaud E, et al. Mitoxantrone versus daunorubicin in induction-consolidation chemotherapy: the value of low-dose cytarabine for maintenance of remission, and an assessment of prognostic factors in acute myeloid leukemia in the elderly: final report. European Organization for the Research and Treatment of Cancer and the Dutch-Belgian Hemato-Oncology Cooperative HOVON Group. *J Clin Oncol*. 1998;16:872-881.

51. Burnett AK, Goldstone AH, Milligan DW, et al. Daunorubicin versus mitoxantrone as induction for AML in younger patients given intensive chemotherapy. Preliminary results of MRC AML-12 trial. *Br J Haematol*. 1999;105(suppl 1):154.

52. Zittoun R, Suciú S, DeWitte T, et al. Comparison of three intercalating agents in induction and consolidation in acute myelogenous leukemia (AML) followed by autologous or allogeneic transplantation: preliminary results of the EORTC-GIMEMA AML-10 randomized trial. *Blood*. 1999;94:2923.

53. Schiller G, Gajewski J, Nimer S, et al. A randomized study of intermediate- versus conventional-dose cytarabine as intensive induction for acute myelogenous leukemia. *Br J Haematol*. 1992;81:170-177.

54. Bishop JF, Matthews JP, Young GA, et

al. A randomized trial of high-dose cytarabine in induction in acute myeloid leukemia. *Blood*. 1996;87:1710-1717.

55. Weick JK, Kopecky KJ, Appelbaum FR, et al. A randomized investigation of high-dose versus standard-dose cytosine arabinoside with daunorubicin in patients with previously untreated acute myeloid leukemia: a Southwest Oncology Group study. *Blood*. 1996;88:2841-2851.

56. Bishop JF, Lowenthal RM, Joshua D, et al. Etoposide in acute nonlymphocytic leukemia. Australian Leukemia Study Group. *Blood*. 1990;75:27-32.

57. Bishop JF, Matthews JP, Young GA, et al. Intensified induction chemotherapy with high dose cytarabine and etoposide for acute myeloid leukemia: a review and updated results of the Australian Leukemia Study Group. *Leuk Lymphoma*. 1998;28:315-327. Review.

58. Hann IM, Stevens RF, Goldstone AH, et al. Randomized comparison of DAT versus ADE as induction chemotherapy in children and younger adults with acute myeloid leukemia. Results of the Medical Research Council's 10th AML trial (MRC AML10). Adult and Childhood Leukaemia Working Parties of the Medical Research Council. *Blood*. 1997;89:2311-2318.

59. Mitus AJ, Miller KB, Schenkien DP, et al. Improved survival for patients with acute myelogenous leukemia. *J Clin Oncol*. 1995;13:560-569.

60. Cassileth PA, Lee SJ, Miller KB, et al. Feasibility study of adding high-dose cytarabine (HDAC) in induction (IND) and in consolidation (CONS) before autologous stem cell transplant (ASCT) in adult acute myeloid leukemia (AML). *Blood*. 1998;92:4559. Abstract.

61. Petersdorf S, Rankin C, Terebolo H, et al. A phase II study of standard dose daunomycin and cytosine arabinoside (Ara-C) with high-dose Ara-C induction therapy followed by sequential high-dose Ara-C consolidation for adults with previously untreated acute myelogenous leukemia: a Southwest Oncology Group study (SWOG 9500). *Proc Annu Meet Am Soc Clin Oncol*. 1998;17:55. Abstract.

62. Buchner T, Hiddemann W, Worman B, et al. Double induction strategy for acute myeloid leukemia: the effect of high-dose cytarabine with mitoxantrone instead of standard-dose cytarabine with daunorubicin and 6-thioguanine: a randomized trial by the German AML Cooperative Group. *Blood*. 1999;93:4116-4124.

63. Buchner T, Hiddemann W, Koenigsmann M, et al. Recombinant human granulocyte-macrophage colony-stimulating fac-

tor after chemotherapy in patients with acute myeloid leukemia at higher age or after relapse. *Blood*. 1991;78:1190-1197.

64. Rowe JM, Andersen J, Mazza JJ, et al. A randomized placebo-controlled phase III study of granulocyte-macrophage colony-stimulating factor in adult patients (>55 to 70 years of age) with acute myelogenous leukemia: a study of the Eastern Cooperative Oncology Group (E1490). *Blood*. 1995;86:457-462.

65. Dombret H, Chastang C, Fenaux P, et al. A controlled study of recombinant human granulocyte colony-stimulating factor in elderly patients after treatment for acute myelogenous leukemia. AML Cooperative Study Group. *N Engl J Med*. 1995;332:1678-1683.

66. Heil G, Hoelzer D, Sanz MA, et al. A randomized, double-blind, placebo-controlled, phase III study of filgrastim in remission induction and consolidation therapy for adults with de novo acute myeloid leukemia: the International Acute Myeloid Leukemia Study Group. *Blood*. 1997;90:4710-4718.

67. Godwin JE, Kopecky KJ, Head DR, et al. A double-blind placebo-controlled trial of granulocyte colony-stimulating factor in elderly patients with previously untreated acute myeloid leukemia: a Southwest Oncology Group study (9031). *Blood*. 1998;91:3607-3615.

68. Stone RM, Berg DT, George SL, et al. Granulocyte-macrophage colony-stimulating factor after initial chemotherapy for elderly patients with primary acute myelogenous leukemia. Cancer and Leukemia Group B. *N Engl J Med*. 1995;332:1671-1677.

69. Zittoun R, Suci S, Mandelli F, et al. Granulocyte-macrophage colony-stimulating factor associated with induction treatment of acute myelogenous leukemia: a randomized trial by the European Organization for Research and Treatment of Cancer Leukemia Cooperative Group. *J Clin Oncol*. 1996;14:2150-2159.

70. Löwenberg B, Suci S, Archimbaud E, et al. Use of recombinant GM-CSF during and after remission induction chemotherapy in patients aged 61 years and older with acute myeloid leukemia: final report of AML-11, a phase III randomized study of the Leukemia Cooperative Group of the European Organisation for the Research and Treatment of Cancer and the Dutch Belgium Hemato-Oncology Cooperative Group. *Blood*. 1997;90:2952-2961.

71. Link H, Wandt H, Schonrock-Nabulski P, et al. G-CSF (Lenograstim) after chemotherapy for acute myeloid leukemia: a placebo controlled trial. *Blood*. 1996;88:2654.

72. Goldstone AH, Burnett AK, Milligan DW, et al. Lack of benefit of G-CSF on complete remission and possible increased relapsed risk in AML: an MRC study of 800 patients. *Blood*. 1997;90:2595.

73. Witz F, Harousseau JL, Sadoun A, et al. GM-CSF during and after remission induction treatment for elderly patients with acute myeloid leukemia (AML). *Hematol Blood Transfus*. 1997;40:852-856.

74. Schiffer CA. Hematopoietic growth factors as adjuncts to the treatment of acute myeloid leukemia. *Blood*. 1996;88:3675-3685.

75. Cassileth PA, Harrington DP, Hines JD, et al. Maintenance chemotherapy prolongs remission duration in adult acute nonlymphocytic leukemia. *J Clin Oncol*. 1988;6:583-587.

76. Robles C, Kim KM, Oken MM, et al. Low-dose cytarabine maintenance therapy vs observation after remission induction in advanced acute myeloid leukemia: an Eastern Cooperative Oncology Group Trial (E5483). *Leukemia*. 2000;14:1349-1353.

77. Buchner T, Hiddemann W, Worman B, et al. Late events in AML: data from long-term observation of patients in two trials starting in 1981 and 1985. *Blood*. 1997;90:2247.

78. Rees JKH, Gray RG, Wheatley K. Dose intensification in acute myeloid leukaemia: greater effectiveness at lower cost: principal report of the Medical Research Council's AML9 study. *Br J Haematol*. 1996;94:89-98.

79. Mayer RJ, Davis RB, Schiffer CA, et al. Intensive postremission chemotherapy in adults with acute myeloid leukemia. Cancer and Leukemia Group B. *N Engl J Med*. 1994;331:896-903.

80. Cassileth PA, Lynch E, Hines JD, et al. Varying intensity of post remission therapy in acute myeloid leukemia. *Blood*. 1992;79:1924-1930.

81. Elonen E, Almqvist A, Hanninen A, et al. Comparison between four and eight cycles of intensive chemotherapy in adult acute myeloid leukemia: a randomized trial of the Finnish Leukemia Group. *Leukemia*. 1998;12:1041-1048.

82. Zittoun RA, Mandelli F, Willemze R, et al. Autologous or allogeneic bone marrow transplantation compared with intensive chemotherapy in acute myelogenous leukemia. European Organization for Research and Treatment of Cancer (EORTC) and the Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto (GIMEMA) Leukemia Cooperative Groups. *N Engl J Med*. 1995;332:217-223.

83. Cassileth P, Harrington D, Paietta E,

- et al. Comparison of autologous bone marrow transplantation (AUTOBMT) with high-dose cytarabine (HDAC) in adult acute myeloid leukemia (AML) in first remission (CR1): an ECOG Intergroup study. *Proc Annu Meet Am Soc Clin Oncol.* 1997;16:311.
84. Harousseau JL, Cahn JY, Pignon B, et al. Comparison of autologous bone marrow transplantation and intensive chemotherapy as postremission therapy in adult acute myeloid leukemia: the Groupe Ouest Est Leucémies Aigues Myéloblastiques (GOE-LAM). *Blood.* 1997;90:2978-2986.
85. Burnett AK, Goldstone AH, Stevens RM, et al. Randomised comparison of addition of autologous bone-marrow transplantation to intensive chemotherapy for acute myeloid leukaemia in first remission: results of MRC AML 10 trial. UK Medical Research Council Adult and Children's Leukaemia Working Parties. *Lancet.* 1998;351:700-708.
86. Soiffer RJ, Fairclough D, Robertson M, et al. CD6-depleted allogeneic bone marrow transplantation for acute leukemia in first complete remission. *Blood.* 1997;89:3039-3047.
87. Papadopoulos EB, Carabasi MH, Castro-Malaspina H, et al. T-cell-depleted allogeneic bone marrow transplantation as postremission therapy for acute myelogenous leukemia: freedom from relapse in the absence of graft-versus-host disease. *Blood.* 1998;91:1083-1090.
88. Cahn JY, Labopin M, Schattenberg A, et al. Allogeneic bone marrow transplantation for acute leukemia in patients over the age of 40 years. Acute Leukemia Working Party of the European Group for Bone Marrow Transplantation (EBMT). *Leukemia.* 1997;11:416-419.
89. Byrd JC, Dodge RK, Carroll A, et al. Patients with t(8;21)(q22;q22) and acute myeloid leukemia have superior failure-free and overall survival when repetitive cycles of high-dose cytarabine are administered. *J Clin Oncol.* 1999;17:3767-3775.
90. Huang ME, Ye YC, Chen SR, et al. Use of all-trans retinoic acid in the treatment of acute promyelocytic leukemia. *Blood.* 1988;72:567-572.
91. Castaigne S, Chomienne C, Daniel MT, et al. All-trans retinoic acid as a differentiation therapy for acute promyelocytic leukemia. I. Clinical results. *Blood.* 1990;76:1704-1709.
92. Warrell RP Jr, Frankel SR, Miller WH Jr, et al. Differentiation therapy of acute promyelocytic leukemia with tretinoin (all-trans-retinoic acid). *N Engl J Med.* 1991;324:1385-1393.
93. Fenaux P, Castaigne S, Dombret H, et al. All-transretinoic acid followed by intensive chemotherapy gives a high complete remission rate and may prolong remissions in newly diagnosed acute promyelocytic leukemia: a pilot study on 26 cases. *Blood.* 1992;80:2176-2181.
94. Chen ZX, Xue YQ, Zhang R, et al. A clinical and experimental study on all-trans retinoic acid-treated acute promyelocytic leukemia patients. *Blood.* 1991;78:1413-1419.
95. Kanamaru A, Takemoto Y, Tanimoto M, et al. All-trans retinoic acid for the treatment of newly diagnosed acute promyelocytic leukemia. Japan Adult Leukemia Study Group. *Blood.* 1995;85:1202-1206.
96. Ohno R, Yoshida H, Fukutani H, et al. Multi-institutional study of all-trans-retinoic acid as a differentiation therapy of refractory acute promyelocytic leukemia. Leukaemia Study Group of the Ministry of Health and Welfare. *Leukemia.* 1993;7:1722-1727.
97. Avvisati G, Lo Coco F, Diverio D, et al. AIDA (all-trans retinoic acid + idarubicin) in newly diagnosed acute promyelocytic leukemia: a Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto (GIMEMA) pilot study. *Blood.* 1996;88:1390-1398.
98. Mandelli F, Diverio D, Avvisati G, et al. Molecular remission in PML/RARalpha-positive acute promyelocytic leukemia by combined all-trans retinoic acid and idarubicin (AIDA) therapy. *Blood.* 1997;90:1014-1021.
99. Sanz MA, Martin G, Rayon C, et al. A modified AIDA protocol with anthracycline-based consolidation results in high antileukemic efficacy and reduced toxicity in newly diagnosed PML/RARalpha-positive acute promyelocytic leukemia. PETHEMA group. *Blood.* 1999;94:3015-3021.
100. Fenaux P, Le Deley MC, Castaigne S, et al. Effect of all transretinoic acid in newly diagnosed acute promyelocytic leukemia. Results of a multicenter randomized trial. European APL 91 Group. *Blood.* 1993;82:3241-3249.
101. Tallman MS, Andersen JW, Schiffer CA, et al. All-trans-retinoic acid in acute promyelocytic leukemia. *N Engl J Med.* 1997;337:1021-1028.
102. De Botton S, Dombret H, Sanz M, et al. Incidence, clinical features, and outcome of all-trans-retinoic acid syndrome in 413 cases of newly diagnosed acute promyelocytic leukemia. The European APL Group. *Blood.* 1998;92:2712-2718.
103. Tallman MS, Andersen JW, Schiffer CA, et al. Clinical description of 44 patients with acute promyelocytic leukemia who developed the retinoic acid syndrome. *Blood.* 2000;95:90-95.
104. Fenaux P, Chastang C, Chevret S, et al. A randomized comparison of all transretinoic acid (ATRA) followed by chemotherapy and ATRA plus chemotherapy and the role of maintenance therapy in newly diagnosed acute promyelocytic leukemia. The European APL Group. *Blood.* 1999;94:1192-1200.
105. Burnett AK, Grimwade D, Solomon E, et al. Presenting white blood cell count and kinetics of molecular remission predict prognosis in acute promyelocytic leukemia treated with all-trans retinoic acid: results of the randomized MRC trial. *Blood.* 1999;93:4131-4143.
106. Sanz MA, Coco FL, Martin G, et al. Definition of relapse risk and role of nonanthracycline drugs for consolidation in patients with acute promyelocytic leukemia: a joint study by the PETHEMA and GIMEMA cooperative groups. *Blood.* 2000;96:1247-1253.
107. Kahn SB, Begg CB, Mazza JJ, et al. Full dose versus attenuated dose daunorubicin, cytosine arabinoside, and 6-thioguanine in the treatment of acute nonlymphocytic leukemia in the elderly. *J Clin Oncol.* 1984;2:865-870.
108. Tucker J, Thomas AE, Gregory WM, et al. Acute myeloid leukemia in elderly adults. *Hematol Oncol.* 1990;8:13-21.
109. Taylor PR, Reid MM, Stark AN, et al. De novo acute myeloid leukaemia in patients over 55 years old: a population-based study of incidence, treatment and outcome. Northern Region Haematology Group. *Leukemia.* 1995;9:231-237.
110. Leith CP, Kopecky KJ, Chen IM, et al. Frequency and clinical significance of the expression of the multidrug resistance proteins MDR1/P-glycoprotein, MRP1 and LRP in acute myeloid leukemia: a Southwest Oncology Group Study. *Blood.* 1999;94:1086-1099.
111. Löwenberg B, Zittoun R, Kerkhofs H, et al. On the value of intensive remission-induction chemotherapy in elderly patients of 65+ years with acute myeloid leukemia: a randomized phase III study of the European Organization for Research and Treatment of Cancer Leukemia Group. *J Clin Oncol.* 1989;7:1268-1274.
112. Tilly H, Castaigne S, Bordessoule D, et al. Low-dose cytosine arabinoside treatment for acute nonlymphocytic leukemia in elderly patients. *Cancer.* 1985;55:1633-1636.
113. Leyden M, Manoharan A, Boyd A, et al. Low dose cytosine arabinoside: partial remission of acute myeloid leukaemia without evidence of differentiation induction. *Br J Haematol.* 1984;57:301-307.

114. Cheson BD, Jasperse DM, Simon R, et al. A critical appraisal of low-dose cytosine arabinoside in patients with acute non-lymphocytic leukemia and myelodysplastic syndromes. *J Clin Oncol.* 1986;4:1857-1864. Review.

115. Rossi Ferini P, Bernabei PA, Leoni F. Low-dose cytosine arabinoside in the treatment of acute non-lymphoblastic leukemia in the elderly. *New Trends Ther Leuk Lymph.* 1986;1:79-85.

116. Powell BL, Capizzi RL, Muss HB, et al. Low-dose ara-C therapy for acute myelogenous leukemia in elderly patients. *Leukemia.* 1989;3:23-28.

117. Detournignies L, Wattel E, Lai JL, et al. Is there still a role for low-dose cytosine arabinoside in de novo acute myeloid leukemia in the elderly? A report on 77 cases. *Ann Hematol.* 1993;66:235-240.

118. Bow EJ, Sutherland JA, Kilpatrick MG, et al. Therapy of untreated acute myeloid leukemia in the elderly: remission-induction using a non-cytarabine-containing regimen of mitoxantrone plus etoposide. *J Clin Oncol.* 1996;14:1345-1352.

119. Tallman MS, Rowlings PA, Milone G, et al. Effect of postremission chemotherapy before human leukocyte antigen-identical sibling transplantation for acute myelogenous leukemia in first complete remission. *Blood.* 2000;96:1254-1258.

120. Gale RP, Horowitz MM, Weiner RS, et al. Impact of cytogenetic abnormalities on outcome of bone marrow transplants in acute myelogenous leukemia in first remission. *Bone Marrow Transplant.* 1995;16:203-208.

121. Ferrant A, Doyen C, Delannoy A, et al. Karyotype in acute myeloblastic leukemia: prognostic significance in a prospective study assessing bone marrow transplantation in first remission. *Bone Marrow Transplant.* 1995;15:685-690.

122. Slovak ML, Kopecky KJ, Cassileth PA, et al. Karyotype analysis predicts outcome of pre- and postremission therapy in adult acute myeloid leukemia (AML): a SWOG/ECOG Intergroup Study. *Blood.* 1998;92:2795.