4. Galmarini CM, Graham K, Thomas X, Calvo F, Rousselot P, El Jafaari A, et al. Expression of high Km 5'-nucleotidase in leukemic blasts is an independent prognostic factor in adults with acute myeloid leukemia. Blood 2001;98:1922-6.
5. Galmarini CM, Thomas X, Graham K, El Jafaari A, Cros E, Jordheim L, et al. Deoxycytidine kinase and cN-II nucleotidase expression in blast cells predict survival in acute myeloid leukaemia patients treated with cytarabine. Br J Haematol 2003;122:53-60.
6. Rampazzo C, Johansson M, Gallinaro L, Ferraro P, Hellman U, Karlsson A, et al. Mammalian 5'(3')-deoxyribonucleotidase, cDNA cloning, and overexpression of the enzyme in Escherichia coli and mammalian cells. J Biol Chem 2000;275:5409-15.
7. Mazzon C, Rampazzo C, Scaini MC, Gallinaro L, Karlsson A, Meier C, et al. Cytosolic and mitochondrial deoxyribonucleotidases: activity with substrate analogs, inhibitors and implications for therapy. Biochem Pharmacol 2003;66:471-9.
8. Galmarini CM, Mackey JR, Dumontet C. Nucleoside analogues: mechanisms of drug resistance and reversal strategies. Leukemia 2001;15:875-90.
9. Amici A, Emanuelli M, Magni G, Raffaelli N, Ruggieri S. Pyrimidine nucleotidases from human erythrocyte possess phosphotransferase activities specific for pyrimidine nucleotides. FEBS Lett 1997;419:263-7.
10. Amici A, Emanuelli M, Raffaelli N, Ruggieri S, Saccucci F, Magni G. Human erythrocyte pyrimidine 5-nucleotidase, PN-I, is identical to p36, a protein associated to lupus inclusion formation in response to α-interferon. Blood 2000;96:1596-8.

Acute Myeloid Leukemia

Differentiating agents + low-dose chemotherapy in the management of old/poor prognosis patients with acute myeloid leukemia or myelodysplastic syndrome

13-cis retinoic acid + $(OH)_2$ vitamin D3 + low-dose 6-thioguanine and cytarabine were tested in 26 patients with acute myeloid leukemia (AML) and in 4 patients with myelodysplastic syndrome (MDS) (median age 72.5), ineligible for standard chemotherapy. The response rate was 50%, with 27% complete remission. The median survival of the whole group and responders was 7.5 (1-47+) and 16.5 months (3.5-47+), respectively.

haematologica 2004; 89:619-620
(*http://www.haematologica.org/journal/2004/5/619)*

Acute myeloid leukemia (AML) and high risk myelodysplastic syndromes (MDS) in patients above the age of 60 usually have an unfavorable outcome.[1-4] In particular, patients unsuitable for standard chemotherapy have a median survival of < 6 months.[3,4] On the basis of previous *in vitro* and *in vivo* observations,[5-7] we treated 26 AML and 4 MDS patients (Table 1), ineligible for intensive chemotherapy because of age, poor clinical conditions or treatment refusal, with a combination of 13-cis retinoic acid (RA) (Roaccutan®, 20-40 mg daily) + $(OH)_2$ vitamin D3 (D3) (Rocaltrol®, 1 μg daily) for 5 weeks, with the addition of 6-thioguanine (6-TG) (Thioguanine®, 40 mg daily) and cytosine arabinoside (ARA-C) (Aracytin®, 8 mg/m^2 × 2/day by subcutaneous injections) during the first 2-3 weeks. After the 5th week of treatment, in the absence of disease progression, the 5-week course was repeated. After the 2nd course the patients were re-assessed. Patients who had obtained at least a partial response continued a maintenance treatment, until disease progression, with RA + D3 + intermittent 6-TG (14-21 days) or ARA-C + 6-mercaptopurine (Purinethol®, 50 mg daily) for 14 days every 5-6 weeks, at the above described dosages.

A complete response (CR) was defined by < 5% bone marrow (BM) blasts with normal cellularity and Hb > 10 g/dL, neutrophils >1.5×10^9/L, and platelets >100×10^9/L. A partial response was defined by the achievement of neutrophil and platelet counts >1×10^9/L and 50×10^9/L, respectively, for at least one month, together with a >50% reduction of BM blasts and/or disappearance of circulating blasts.

Remission duration and survival were calculated by Kaplan-Meier curves.[8] The treatment was reasonably well tolerated: grade 4 neutropenia and thrombocytopenia were observed in 28 patients (94%) during the first two courses of low-dose chemotherapy and 4 patients (13%) aged > 75 died of neutropenia-related infections. Thirteen patients completed the induction treatment as outpatients, while 17 were hospitalized for a median time of 18 days (5-45). Eleven of the 30 patients required intravenous antibiotics and 2 required G-CSF administration for prolonged neutropenia. In responsive patients, the median time to reach neutrophil and platelet values above 0.5 and 20×10^9/L,

Table 1. Patients' clinical features.

	AML	*MDS*
Sex	M 17 F 9	M 3 F 1
Age[1] (years)	72.5 (41-88)	69.5 (61-84)
Age Distribution	<60 2 60-70 8 71-80 13 >80 3	60-70 2 >70 2
Diagnosis[2]	M1 6 M2 10 M4 7 M5a 2 M7 1	RAEB 2 4
Secondary Disease	Post MDS 7 Post chronic MPD 2 Therapy related 1 All 10/26	 Therapy related 1 All 1/4
Disease status	Diagnosis 21 1st relapse 2 2nd relapse 1 3rd relapse 2	Diagnosis 4
Karyotype	Normal 7 Abnormal 4 N.E. 15	Normal 2 Abnormal 2
WBC[1]×10^9/L	3.8 (1.5-93)	2.5 (0.9-3.8)
WBC > 20×10^9/L	4/26	
IPSS[3]	N.E.	Intermediate[2] (2 patients with intermediate 2 score) High 2

[1]: median value and (range); [2]: diagnosis according to FAB and WHO classification; [3]: International Prognostic Scoring System.

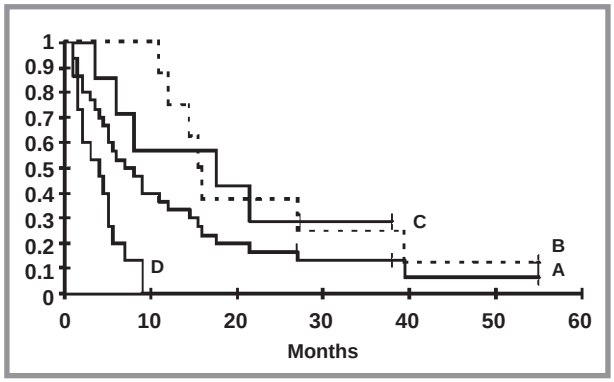

Figure 1. Overall survival, calculated from diagnosis or last relapse to death. Patients were cumulatively evaluated and separated according to treatment response. A: all patients, B: complete responders, C: partial responders, D: non-responders. Differences between B and D and between C and D are both statistically signicant (p = < 0.001). Differences between B and C are not significant.

respectively, was 20 (0-90) and 21 days (0-92). Patients who achieved a response tolerated maintenance treatments without severe hematologic toxicity. Non- hematologic toxicity included frequent, mild lip and oral dryness. Moderate nausea and grade 1-2 hepatic toxicity occurred sporadically. No patient required parenteral nutrition for severe mucositis. Fifteen patients (50%) responded to therapy; in particular, 8 (27%) obtained a CR and 7 (23%) a PR. Morphologic features of dysplastic hematopoiesis remained evident in 7/15 responsive patients. The median response duration and survival both reached 7.5 months (range: 1-33 and 1-51+, respectively) (Figure 1) and actual 2-year survival was 17%. The whole group of responsive (CR+PR) patients survived considerably longer (median: 16.5 months, range 3-54+, 34% alive at 2 years) than non responders (median 4 months, range 1-9) ($p < 0.001$), without significant differences between CR and PR patients (Figure 1). The aim of this study, adding low dose ARA-C to the former protocol, was to provide an acceptable treatment for AML patients ineligible for intensive chemotherapy. In spite of the few cytogenetic analyses performed and chromosomal abnormalities found, all patients presented quite prognostically unfavorable features. As expected from the use of ARA-C and the high blast percentage, hematologic toxicity was pronounced during induction therapy. However, therapy- related mortality (13%) was in the range reported previously for the low-dose ARA-C alone,[9] whereas response rate and survival were somewhat higher. Toxicity was acceptable and responsive patients showed a clear survival advantage over non-responders and a historical series of patients treated with supportive care only. Remarkably, CR achievement was not an absolute requirement to obtain a survival benefit, since a partial response could often be maintained for several months. The results of this study indicate that our combination of RA + D3 + low dose chemotherapy can be useful for AML patients ineligible for intensive chemotherapy. These encouraging results do, of course, need to be confirmed in larger series.

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Key words: AML, myelodysplastic syndrome, differentiating therapy

Funding: the study was partially supported by Università degli Studi di Torino (ex 60% funds). We thank Roche for freely providing part of the Roaccutan® and the Rocaltrol® used throughout the study. Part of preliminary results of this study were presented as an "abstract" at the meeting of "Società Italiana di Ematologia Sperimentale", 2002.

References

1. Sekeres MA, Stone RM. The challenge of acute myeloid leukemia in older patients. Curr Opin Oncol 2002;14:24-30.
2. Verbeek W, Ganser A. Evolving treatment options of myelodysplastic syndromes. Ann Hematol 2001;80:499-509.
3. Veneri D, Zanetti F, Franchini M, Ambrosetti A, Pizzolo G. Acute myeloid leukemia in the elderly: evaluation of overall survival in 69 consecutive patients. Haematologica 2002;87:447-8.
4. Ferrara F, Annunziata M, Copia C, Magrin S, Mele G, Mirto S. Therapeutic options and treatment results for patients over 75 years of age with acute myeloid leukemia. Haematologica 1998; 83:126-31.
5. Ferrero D, Carlesso N, Bresso P, Roux V, Pregno P, Gallo E, et al. Suppression of in vitro maintenance of non-promyelocytic myeloid leukemia clonogenic cells by all-trans retinoic acid: modulating effects of dihydroxylated vitamin D3, α interferon and "stem cell factor". Leuk Res 1997;21:51-8.
6. Tawhid H, Rees J. Triple combination of retinoic acid + 6-thioguanine + hexamethylene bisacetamide induces differentiation of human AML blasts in primary culture. Leuk Res 1990;14:109-17.
7. Ferrero D, Bruno B, Pregno P, Stefani S, Larizza E, Ciravegna G, et al. Combined differentiating therapy for myelodysplastic syndromes: a phase II study. Leuk Res 1996;20:867-76.
8. Kaplan EL, Meier P. Non parametric estimation from incomplete observations. J Am Stat Assoc 1958; 53:457-81.
9. Miller KB, Kim K, Morrison FS, Winter JN, Bennett JM, Neiman RS, et al. The evaluation of low-dose cytarabine in the treatment of myelodysplastic syndromes: a phase-III intergroup study. Ann Hematol 1992;65:162-8.
10. Greenberg P, Cox C, LeBeau MM, Fenaux P, Morel P, Sanz G, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood 1997;89:2079-88.