ics of STI571 in a phase 1 trial in chronic myelogenous leukemia (CML) patients. Proc Am Assoc Cancer Res 2000;41:3468[abstract].
4. Druker BJ, Lydon NB. Lessons learned from the development of an Abl tyrosine kinase inhibitor for chronic myelogenous leukemia. J Clin Invest 2000;105:3-7.
5. Marin D, Marktel S, Bua M, Olavarria E, Apperley J, Goldman JM. The combination of cytogenetic response after 6 months treatment with STI571 and the presence of cytopenias in patients with CML in chronic phase resistant to or intolerant of interferon-α defines four different prognostic groups. Blood 2001;98:3514a[abstract].
6. Marin D, Marktel S, Bua M, Armstrong L, Goldman JM, Apperley JF, et al. The use of imatinib (STI571) in chronic myeloid leukemia: some practical considerations. Haematologica 2002;87:979-88.
7. Kantarjian HM, Dixon D, Keating MJ, Talpaz M, Walters RS, McCredie KB, et al. Characteristics of accelerated disease in chronic myelogenous leukemia. Cancer 1988;61:1441-6.

Oral induction and consolidation chemotherapy with idarubicin and etoposide in elderly patients with acute myeloid leukemia

Exploring tolerable regimes for the treatment of acute myeloid leukemia (AML) in elderly patients is of interest. Twenty-two adults over 70 years of age with AML were treated with an oral schedule of idarubicin (30 mg/m^2/d) and etoposide (45 mg/m^2/d) for three consecutive days. Seven (32%) achieved complete remission, seven (32%) showed absolute resistance and eight (36%) died. The survival probability one year after diagnosis was 14%. Results are comparable to those described for standard intravenous regimens.

haematologica 2003; 88:229-230
(*http://www.haematologica.org/2003_02/88229.htm*)

Exploring more tolerable regimens is of interest in elderly patients (i.e. patients older than 70 years) with AML. The clinical status of some patients allows the use of standard full-scale intensive treatments but such chemotherapy results in excessive toxicity for most.[1] The aims of this study were to evaluate the feasibility of an oral induction and consolidation regimen with idarubicin and etoposide in elderly patients with AML and to determine the outcome of the patients treated in this way.

Patients 70 years of age or older with untreated *de novo* AML were eligible. Patients with acute promyelocytic leukemia, a prior history of myelodysplasia, or pre-existing severe conditions were excluded. The induction regimen consisted of oral idarubicin (30 mg/m^2 per day) and oral etoposide (45 mg/m^2 per day) for three consecutive days (1 to 3). Patients who obtained a partial remission (reduction to at least 50% of the initial marrow blast percentage) received a second induction course. Patients who did not obtain a complete remission (CR) after one or two induction cycles were removed from the study. Patients in CR were assigned to receive three consolidation courses of idarubicin and etoposide at the same doses used for induction approximately every 28 days or at least 1 week after peripheral blood recovery.

From January 1999 to December 2000, a total of 74 patients were diagnosed with *de novo* AML. Fifty-two patients were considered ineligible because of a poor performance status or associated conditions. Twenty-two patients (30%) were included in the study and treated (Table 1). Eight patients (36%), died during treatment-induced marrow hypoplasia and 7 (32%)

Table 1. Characteristics of the 22 elderly AML patients and toxicity of the treatment schedule.

Sex	Male/female	16/6
Age (years)	Median (range)	73 (70-89)
Performance status	ECOG 0-1 / 2-3	11/11
Leukocytes (×10^9/L)	Median (range)	6 (2-140)
Hemoglobin (g/L)	Median (range)	96 (42-122)
Platelets (×10^9/L)	Median (range)	77 (23-675)
AML Subtype	Myeloid with/without maturation	13
	Myelomonocytic/monocytic	6
	Other morphologic subtypes	3
Cytogenetics	Good risk[1]	3
	Intermediate	10
	High risk	2
	Unavailable	7

Treatment Schedule		*Induction*	*Consolidation*
Patients (evaluable courses)		*22 (27)*	*7 (12)*
Days of neutropenia[2]	Median (range)	21 (10-38)	15 (12-28)
Days of thrombocytopenia[3]	Median (range)	23 (10-65)	16 (8-25)
Major hemorrhage	Events (deaths)	4 (2)	2 (0)
Major infection	Events (deaths)	10 (4)	2 (1)
Other major toxicity (WHO grades 3-4)			
Mucositis/digestive		3	1
Respiratory		1[4]	–
Neurologic		1[4]	–

[1]"Good-risk" cytogenetics was associated with other alterations in the 3 cases: t(8;21)+del(9p), inv(16)+del(9)+add(17p) and inv(16)+trisomy 22. AML cytogenetic and morphologic subtype according to MRC[2] and WHO[10] criteria. [2]<0.5×10^9/L. [3]<20×10^9/L. [4]Pulmonary and cerebral hemorrhage. The same cases are also included in the major hemorrhage count, accounting for both deaths.

were withdrawn because of resistance after one or two induction cycles. The CR rate was 32%. The median (range) time to neutrophil count > 0.5×10^9/L was 21(10-38) days and to platelet count >20×10^9/L 23 (10-65) days (Table 1). Four CR patients (18%) received all the courses of consolidation therapy. Treatment was discontinued because of toxicity after induction in two patients. The median follow-up from diagnosis was 20 months. The probability of remaining alive one year after diagnosis was 14% (95% CI 1-20%), and the probability of being alive and disease-free for patients achieving CR after one year was 28% (95% CI; 0-60%) (Figure 1).

AML in aged patients is characterized by unfavorable prognostic features which are related not only to the patient's status but also to the disease.[1,3,4] Underlying diseases, organ dysfunction and poor tolerance of intensive treatment prevent most patients from entering clinical studies. Despite the substantial toxicity associated with antileukemic therapy, there is general agreement that cytotoxic chemotherapy is still the treatment of choice[5,6] although it is feasible for a minority of patients. The study protocol herein reported was designed to allow the inclusion of a greater proportion of elderly patients while still aiming to obtain and maintain CR. The drugs and route of administration had been tested before, although at lower doses, with encouraging results.[7,8] Thirty percent of all AML patients 70 years or older were treated. The first interim analysis revealed two facts that prompted discontinuation of the study. The first was a high rate of early deaths (36%). Hematologic toxicity was similar to any standard 3+7+3

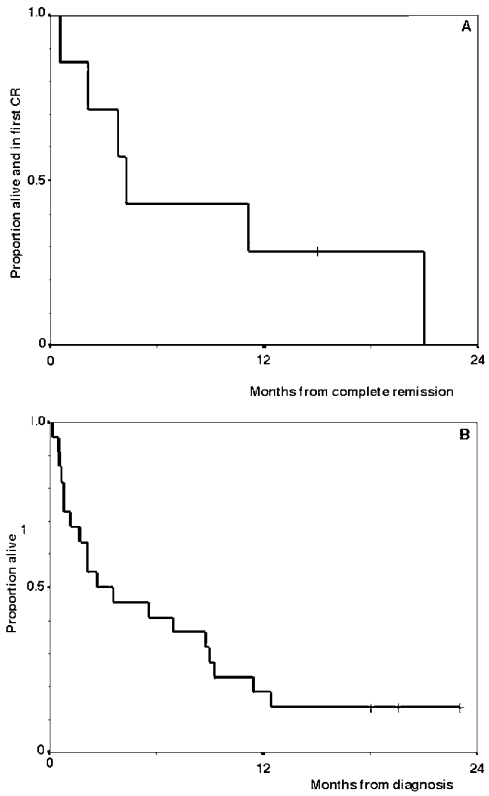

Figure 1. Panel A. Probability of disease-free survival for patients with complete response. The median follow-up was 15 months. Tick marks indicate alive patients in continuous complete remission. Panel B. Probability of survival for all patients. The median follow-up was 20 months. Tick marks indicate alive patients.

treatment and this toxicity was not counterbalanced by a higher remission rate (32%). The second fact was that although the disease-free survival and overall survival results are consistent with those described in other series,[5,6] there was no evidence of any benefit in survival over standard intravenous regimens. These results are in contrast with those from other groups,[7,8] who reported acceptable remission rates with oral idarubicin and etoposide, with idarubicin given at half the dose used in our protocol. Thus, in patients over 70 years with *de novo* AML, standard intravenous regimens should still be recommended for the very small group of patients who are candidates for intensive therapy. New investigational drugs and approaches should be used in uniform subgroups of the remaining patients.

Albert Oriol, Josep-Maria Ribera, Salut Brunet, Jordi Esteve, Javier Bueno, Andrés Llorente, on behalf of the CETLAM Group, Catalonia, Spain

Correspondence: Albert Oriol, Servei d'Hematologia, Hospital Universitari Germans Trias i Pujol, Ctra. Del Canyet s/n, 08916 Badalona, Barcelona, Spain. Phone: international +34.9.34978987. Fax: international +34.9.34978995. E-mail: jmribera@ns.hugtip.scs.es

Key words: acute myeloid leukemia, elderly patients, oral chemotherapy, survival.

Acknowledgments: The following institutions and physicians provided support to the investigators of the CETLAM group and participated in the present trial: Hospital Universitari Germans Trias i Pujol, Badalona (A. Oriol, JM. Ribera); Hospital de la Santa Creu i Sant Pau, Barcelona (S. Brunet, J. Sierra); Hospital Clínic, Barcelona (J. Esteve, E. Montserrat); Hospital Vall d'Hebron, Barcelona (J. Bueno, A. Julià); Institut Català d'Oncologia, Barcelona (J. Berlanga, A. Grañena); Hospital del Mar, Barcelona (C. Pedro); Hospital Joan XXIII, Tarragona (A. Llorente); Hospital Josep Trueta, Girona (J. Guàrdia); Hospital Verge de la Cinta, Tortosa (LI. Font); Hospital Clínico Universitario, Valencia (M. Tormo); Hospital Arnau de Vilanova, Lleida (JM. Sanchez).

Funding: supported in part by grant P-EF-01 from Fundación Internacional José Carreras para la Lucha contra la Leucemia, and Xarxa Temàtica Dinamitzadora 2000-XT/00026 from Generalitat de Catalunya.

Manuscript processing

This manuscript was peer-reviewed by two external referees and by Dr. Elihu Estey, who acted as an Associate Editor. The final decision to accept this paper for publication was taken jointly by Dr. Estey and the Editors. Manuscript received February 4, 2002; accepted November 27, 2002.

References

1. 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.
2. Grimwade D, Walker H, Oliver F, Wheatley K, Harrison C, Harrison G, 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 Leukaemia Working Parties. Blood 1998;92:2322-33.
3. Hiddemann W, Kern W, Schoch C, Fonatsch C, Heinecke A, Wormann B, et al. Management of acute myeloid leukemia in elderly patients. J Clin Oncol 1999;17:3569-76.
4. Venditti A, Del Poeta G, Buccisano F, Tamburini A, Cox-Froncillo MC, Bruno A, et al. Biological features of acute myeloid leukemia in the elderly. Blood 1998;92:697-9.
5. Goldstone AH, Burnett AK, Wheatley K, Smith AG, Hutchinson RM, Clark RE. Attempts to improve treatment outcomes in acute myeloid leukemia (AML) in older patients: the results of the United Kingdom Medical Research Council AML11 trial. Blood 2001;98:1302-11.
6. Kahn SB, Ebrahim K, Cassileth P, Bennett JM, Knospe WH, O'Connell MJ. Attenuated high-dose cytosine arabinoside in the treatment of the elderly patient with acute nonlymphocytic leukemia. An Eastern Cooperative Oncology Group Pilot Study. Am J Clin Oncol 1989;12:201-4.
7. Ruutu T, Elonen E. Etoposide, 6-thioguanine and idarubicin, an oral combination regimen (ETI) for the induction treatment of acute leukemia. Hematol Oncol 1991;9:87-92.
8. Ruutu T, Almqvist A, Hallman H, Honkanen T, Jarvenpaa E, Jarventie G, et al. Oral induction and consolidation of acute myeloid leukemia with etoposide, 6-thioguanine, and idarubicin (ETI) in elderly patients: a randomized comparison with 5-day TAD. Finnish Leukemia Group. Leukemia 1994;8:11-5.
9. Grimwade D, Walker H, Harrison G, Oliver F, Chatters S, Harrison CJ, et al. The predictive value of hierarchical cytogenetic classification in older adults with acute myeloid leukemia (AML): analysis of 1065 patients entered into the United Kingdom Medical Research Council AML11 trial. Blood 2001;98:1312-20.
10. Jaffe ES, Harris NL, Stein H, Vardiman JW, editors. World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues. Lyon: IARC Press;2001.