

Hematopoietic stem cell transplantation for de novo erythroleukemia: a study of the European Group for Blood and Marrow Transplantation (EBMT)

Loïc Fouillard, Myriam Labopin, Norbert-Claude Gorin, Emmanuelle Polge, Hugh Grant Prentice, Giovanna Meloni, Josy Reiffers, Arnaud Pigneux, Roel Willemze, Anton Schattenberg, Simona Sica, Monique Lagrange, Odile Fenneteau, Christine Perot, and Francesco Frassoni, for the Acute Leukemia Working Party of the EBMT

De novo erythroleukemia (EL) is a rare disease. Reported median survival are poor and vary from 4 to 14 months. The value of hematopoietic stem cell transplantation (HSCT) for EL is unknown. This EBMT registry study reports on the largest series of patients with EL treated with HSCT in first complete remission—103 autologous and 104 HLA identical sibling allogeneic HSCT. Outcome and

identification of prognostic factors for each type of transplantation were evaluated. For autologous HSCT, outcome at 5 years showed a leukemia-free survival (LFS) of $26\% \pm 5\%$, a relapse incidence (RI) of $70\% \pm 6\%$, and a transplant-related mortality (TRM) of $13\% \pm 4\%$. By multivariate analysis, the only prognostic factor was age. For allogeneic HSCT, outcome at 5 years showed an LFS of $57\% \pm 5\%$,

an RI of $21\% \pm 5\%$, and a TRM of $27\% \pm 5\%$. By multivariate analysis, prognostic factors were graft-versus-host disease and age. This study represents the largest series of de novo EL treated with HSCT and shows that allogeneic HSCT is by far the most effective treatment. (Blood. 2002;100:3135-3140)

© 2002 by The American Society of Hematology

Introduction

Erythroleukemia (EL) is an uncommon form of acute myeloblastic leukemia that was recognized in 1912 by Copelli¹ as a hematologic disorder named erythematosis. In 1917, Di Guglielmo² reported additional observations of a neoplastic disorder with proliferation of the erythroid precursors and involvement of the granulocytic series. In 1940, Moeschlin³ definitively established the term erythroleukemia, and later, Dameshek proposed the term Di Guglielmo's syndrome⁴ describing 3 sequential phases of morphologic alteration within the bone marrow: an erythremic phase, an erythromyeloblastic phase, and a myeloblastic phase indistinguishable from acute myeloblastic leukemia.⁵

In 1976, the French-American-British (FAB) cooperative group classified EL as acute myeloid leukemia (AML) M6.⁶ In fact, criteria for diagnosis of AML M6 were confused with myelodysplastic syndrome, megaloblastic anemia, congenital dyserythropoietic anemia, and secondary acute leukemia. Finally, the 1985 revised FAB classification defined EL as leukemia comprising an erythroid component of at least 50% and a myeloid component of at least 30% of the nonerythroid cells.⁷

EL represents only 1% to 3% of all leukemias and 4.5% of all AMLs. The age range of patients with EL is 2 to 85 years, with a median in the fifth and sixth decades.⁸ EL is de novo for approximately half of patients, or secondary to myelodysplastic syndrome or chemotherapy and is frequently associated with multiple chromosomal abnormalities.⁹ It has been reported that EL is less sensitive to chemotherapy than other AML subtypes,

that median survival varies from 4 to 14 months,^{8,10-15} and that it has a tendency to transform into other AML subtypes.⁹

Whereas the benefit of high-dose therapy with autologous or allogeneic hematopoietic stem cell transplantation (HSCT) for AML is now well established by several randomized studies comparing chemotherapy to autologous or allogeneic HSCT,¹⁶⁻²⁰ the real value of high-dose therapy with HSCT for EL is unknown. In this study we used the prospectively collected data of the EBMT acute leukemia registry to analyze the fate of patients with de novo EL who underwent transplantation while in first complete remission (CR1). This study reports the largest series of patients with such a rare disease treated with autologous or allogeneic HSCT.

Patients, materials, and methods

Patients

The study concerned patients receiving transplants from January 1986 to December 2000 in 117 European centers, and consisted of patients older than 16 years with de novo EL who underwent transplantation in CR1. Results were reported to the Acute Leukemia (AL) registry of the EBMT. Secondary acute leukemias were usually reported to the EBMT Chronic Leukemia Registry, and familial ELs were not included.

EBMT teams are supposed to submit consecutive cases, though for logistic reasons this was not the case for all teams throughout the observation period from 1979 to 2000. Since 1996, EBMT is annually

From the Centre International Greffe de Moelle (EBMT), Centre de Recherche Claude Bernard sur la Thérapie Cellulaire, Université Pierre et Marie Curie Paris VI: Institut des Cordeliers, Paris; Department of Hematology, Laboratory of Hematology, and Laboratory of Cytogenetics, Hôpital Saint-Antoine, Paris; Laboratory of Hematology, Hôpital Robert Debré, Paris; CHU Bordeaux, Hôpital Haut Lévêque, Pessac, France; Department of Haematology, Royal Free Hospital and University College Medical School, London, England; Dipartimento di Biotecnologie Cellulari e Ematologica, University La Sapienza, Rome; Department of Hematology, Università Cattolica S Cuore, Rome; Department of Hematology, Ospedale San Martino, Genoa, Italy; BMT Centre Leiden, Leiden University Hospital; and Medical Centre, Nijmegen,

The Netherlands.

Submitted November 29, 2001; accepted June 13, 2002.

Reprints: Loïc Fouillard, Service des maladies du sang, Hôpital Saint-Antoine, 184 rue du faubourg Saint-Antoine, 75571 Paris Cedex 12, France; e-mail: fouillar@ext.jussieu.fr.

The publication costs of this article were defrayed in part by page charge payment. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance with 18 U.S.C. section 1734.

© 2002 by The American Society of Hematology

subjected to a possible audit program. Participating institutions are listed in Appendix 1.

The AL registry contained information on 312 adult patients with de novo EL who were registered from January 1986, with the AML M6 FAB subtype according to the 1985 revised FAB classification. Among these, 207 patients underwent HSCT while in CR1—103 autologous HSCT and 104 HLA identical sibling allogeneic HSCT.

To ensure the reliability of the diagnosis of EL, a subset of 92 (43.6%) initial diagnostic marrow aspirates was reviewed by a panel of experts to confirm the diagnosis of EL according to the 1985 revised FAB classification. Confirmation in this subset was obtained in 95.6% of the cases.

Cytogenetics data were available in the registry for 112 patients. Information on karyotype analysis was given as not performed, failed, normal, or abnormal.

Statistical analysis

The aim of this study was to evaluate the outcome of patients with de novo EL in CR1 undergoing autologous HSCT or HLA identical sibling allogeneic HSCT and to identify prognostic factors for autologous and allogeneic HSCT. It is not a comparative study between autologous and allogeneic HSCT for AML but a study demonstrating actual outcome of a rare disease (EL) treated with high-dose therapy and HSCT.

All analyses were performed using the SPSS computer program (SPSS, Chicago, IL). Values reported for quantitative variables were median and range.

For all analyses, continuous variables were categorized as follows: each variable was first divided into 5 categories at approximately the 20th, 40th, 60th, and 80th percentiles. If the relative event rates (ratio of the observed number of events to the expected number of events in a category assuming no variation across categories) in 2 or more adjacent categories (and the mean times-to-event) were not substantially different, these categories were grouped. If a linear trend was observed in the relative event rates, the variable was used as a continuous factor. Otherwise, the median was used as a cut-off point.

Leukemia-free survival (LFS) was defined as survival without evidence of relapse; the event under study was death or relapse. Relapse was defined as hematologic recurrence at any site. To evaluate the probability of relapse incidence (RI), patients dying from direct toxicity of the procedure or from any other cause not related to leukemia were censored. Transplant-related mortality (TRM) was defined as death occurring in continuous CR after HSCT.

Patients were censored at the time of relapse or at last follow-up. Probabilities of LFS, RI, and TRM were estimated by the product-limit method.²¹ By univariate analysis, the following variables were analyzed: patient age and sex, leukocyte count at diagnosis, year of transplantation, time from diagnosis to CR1, time from CR1 to HSCT, total body irradiation (TBI), busulfan or other chemotherapy in the conditioning regimen, and source of stem cells. Acute graft-versus-host disease (GVHD) for allogeneic HSCT was included in the model as a time-dependent covariate. The significance of differences between curves was estimated by the log-rank test (Mantel-Cox). All variables associated with outcomes with $P < .1$ in univariate analysis were included in a multivariate analysis. Then a backward stepwise procedure was used to select the covariates ($P \leq .05$) included in the Cox proportional hazards model.²²

Results

Distribution of patients receiving autologous HSC transplants

One hundred three patients underwent high-dose therapy followed by autologous HSCT (Table 1). The median age was 40 years (range, 17-69 years), the male/female ratio was 57:46, and the median leukocyte count at diagnosis was $3.8 \times 10^9/L$ (range, $0.9 \times 10^9/L$ - $32 \times 10^9/L$).

Median time from diagnosis to CR1 was 44 days (range, 24-199 days), and from CR1 to autologous HSCT 120 days (range, 37-324

days). TBI was part of the conditioning regimen for 26% of patients, and busulfan for 38% of patients.

The source of stem cells was bone marrow in 51% of patients, peripheral blood in 43% of patients, and both in 6% of patients. Bone marrow was used from 1986 and peripheral blood from 1990.

Distribution of patients receiving HLA identical sibling allogeneic HSC transplants

One hundred four patients received high-dose therapy followed by allogeneic transplantation from an HLA identical sibling donor (Table 1). The median age was 36 years (range, 16-63 years), the male/female ratio was 54:50, and the median leukocyte count at diagnosis was $3 \times 10^9/L$ (range, $0.8 \times 10^9/L$ - $200 \times 10^9/L$).

Median time from diagnosis to CR1 was 47 days (range, 21-245 days), and from CR1 to HSCT 99 days (range, 10-351 days). Conditioning regimen was TBI for 56% of patients and busulfan for 31% of patients.

The source of stem cells was bone marrow in 74% of patients, peripheral blood in 23% of patients, and both in 3% of patients. Bone marrow was used from 1986 and peripheral blood from 1995. For GVHD prophylaxis, a combination of cyclosporin A and methotrexate was used in 62% of patients, T-cell depletion in 22%, and other types of prophylaxis in 17% of patients.

Cytogenetics analysis

Information on cytogenetics was available in 112 patients. In 27 patients karyotype analysis technically failed or was not performed.

In the remaining 85 evaluable patients, 52 had no chromosomal abnormalities and 33 had chromosomal abnormalities (described in only 27). For the 79 (52 + 27) informative patients, cytogenetics were reclassified according to Southwest Oncology Group (SWOG) as favorable, intermediate, unfavorable, and unknown¹⁷; 43 patients underwent allogeneic HSCT and 36 underwent autologous HSCT. Results are shown in Table 2.

Table 1. Distribution of adult patients with de novo EL treated by autologous or identical sibling allogeneic HSCT in first CR

	Autologous HSCT (103 patients)	Identical sibling allogeneic HSCT (104 patients)
Median age, y (range)	40 (17-69)	36 (16-63)
Male/female ratio	57:46	54:50
Median leukocyte count at diagnosis, $\times 10^9/L$ (range)	3.8 (0.9-32)	3 (0.8-200)
Median time from diagnosis to CR1, d (range)	44 (24-199)	47 (21-245)
Median time from CR1 to HSCT, d (range)	120 (37-324)	99 (10-351)
Conditioning regimen, %		
With TBI	26	56
With busulfan	38	31
Other chemotherapy alone	26	9
Missing data	10	5
Source of stem cells, %		
Bone marrow	51	74
Peripheral blood	43	23
Both	6	3
GVHD prophylaxis, %		
Cyclosporin + methotrexate	—	62
T-cell depletion	—	22
Other	—	17

Table 2. HSCT for adult de novo EL in first CR

Cytogenetic risk groups (SWOG criteria)	Identical-sibling allogeneic HSCT n = 43	Autologous HSCT n = 36
Favorable n = 0	n = 0	n = 0
Intermediate n = 58	Normal, n = 28 Trisomy 8, n = 2	Normal, n = 24 Trisomy 8, n = 4
Unfavorable n = 12	n = 8 abn 3q and 9q abn 11q del(7)	n = 4 abn 20q and t(5;7),del(17q) -7 in complex karyotype abn 3q, -7, and ins(6p) del(5q),-7, abn 17p in complex karyotype
Unknown n = 9	n = 5 i(18q) Pseudo/hypodiploidy del(6) -20,+mar Hypodiploidy	n = 4 Tetraploidy Hypodiploidy Hypodiploidy Pseudo near-triploidy and tetraploidy

Results of karyotype at diagnosis classified according to the SWOG cytogenetics risk groups in 79 informative patients—52 with normal karyotype and 27 with abnormal karyotype.

Outcome following autologous HSCT

Median follow-up was 26 months (range, 1-157 months). The outcome at 5 years showed an LFS of 26% ± 5% (Figure 1), an RI of 70% ± 6% (Figure 2), a TRM of 13% ± 4%, and an overall survival (OS) of 34% ± 6%. Forty-four patients died of EL relapse, and 11 patients died of toxicity (5 infections, 1 graft failure, 3 hemorrhage, and 1 interstitial pneumonitis); information was missing for 2 patients.

Outcome following allogeneic identical sibling HSCT

Median follow-up was 46 months (range, 2-169 months). The outcome at 5 years showed an LFS of 57% ± 5% (Figure 3), an RI of 21% ± 5% (Figure 4), a TRM of 27% ± 5%, and an OS of 57% ± 5%. Seventeen patients died of EL relapse, and 26 died of toxicity (8 infections, 8 GVHD, 3 interstitial pneumonitis, 1 hemorrhage); information was missing for 6 patients.

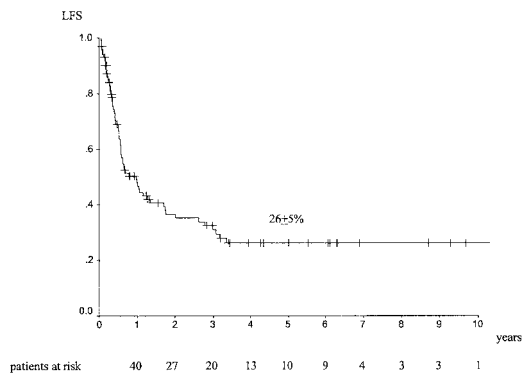


Figure 1. LFS at 5 years in adult patients with de novo EL treated with autologous HSCT in CR1.

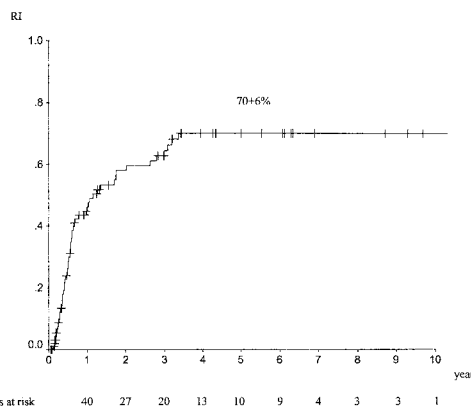


Figure 2. RI at 5 years in adult patients with de novo EL treated with autologous HSCT in CR1.

Acute GVHD of grade 2 or more developed in 36% of patients. Of 87 patients alive and well at 100 days after transplantation, chronic GVHD developed in 41% (limited in 24% and extensive in 17%) of patients.

Prognostic factors

For autologous HSCT, univariate analyses indicated that ages below the median of 40 years was associated with a better LFS (34% ± 8% vs 19% ± 6%; *P* = .04), a trend for a lower RI (61% ± 8% vs 79% ± 7%; *P* = .08), and better survival (44% ± 8% vs 24% ± 7%; *P* = .045). Peripheral blood transplantation was associated with a trend for a lower TRM (5% ± 3% vs 20% ± 6%; *P* = .09). There was no statistical difference on LFS (23% ± 9% vs 27% ± 6%; *P* = .91) and on RI (76% ± 9% vs 66% ± 8%; *P* = .35) between peripheral blood and bone marrow. A conditioning regimen with TBI was associated with a better LFS than regimens containing busulfan or consisting of other chemotherapies (40% ± 10% vs 32% ± 8% vs 24% ± 9%; *P* = .03), respectively. With TBI, there was a trend for lower RI (63% ± 11% vs 67% ± 9% vs 79% ± 9%; *P* = .06). Using multivariate analysis, young age below the median value was associated with a better LFS (relative risk [RR] = 1.67 [1.02-2.73]; *P* = .044) and better OS (RR = 1.74 [1.01-3.04]; *P* = .05).

For allogeneic HSCT, univariate analyses indicated that female patients had a trend for a better LFS (67% ± 7% vs 49% ± 7%; *P* = .09). Acute GVHD of grade 2 or more was associated with a lower LFS (45% ± 8% vs 64% ± 6%; *P* = .053), a higher TRM (38% ± 8% vs 21% ± 6%; *P* = .07), and a lower OS (44% ± 8%

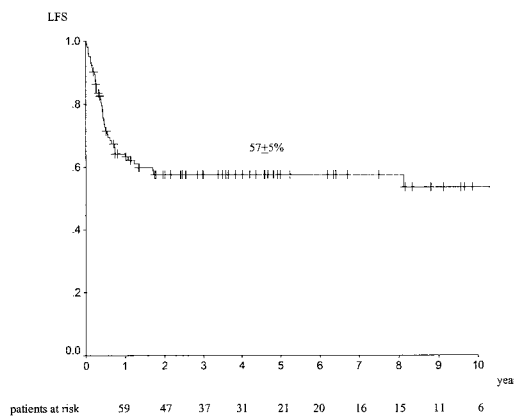


Figure 3. LFS at 5 years in adult patients with de novo EL treated with identical sibling allogeneic HSCT in CR1.

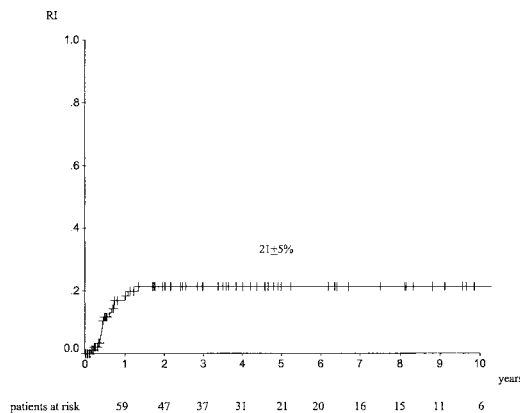


Figure 4. RI at 5 years in adult patients with de novo EL treated with allogeneic identical sibling HSCT in CR1.

vs $63\% \pm 7\%$; $P = .047$). Seventy-six patients aged 45 years and younger had a statistically significant better outcome than 26 patients older than 45 years. LFS was $64\% \pm 6\%$ and $42\% \pm 10\%$ ($P = .02$), TRM was $23\% \pm 5\%$ and $39\% \pm 11\%$ ($P = .06$), and OS was $63\% \pm 6\%$ and $39\% \pm 11\%$ ($P = .014$), respectively. No difference was found on RI— $17\% \pm 5\%$ and $31\% \pm 11\%$ ($P = .15$), respectively. By multivariate analysis, acute GVHD of grade 2 or more was associated with higher TRM (RR = 2.65 [1.17-6.02]; $P = .02$). Age older than 45 years was associated with lower LFS (RR = 2.1 [1.12-3.94]; $P = .02$), higher TRM (RR = 2.58 [1.16-5.74]; $P = .02$), and lower OS (RR = 2.14 [1.15-4.01]; $P = .017$).

Discussion

This EBMT study on 207 adult patients with de novo EL who underwent transplantation in CR1 indicates that HLA identical sibling allogeneic HSCT can cure more than 50% of patients. Indeed, the LFS at 5 years after allogeneic transplantation was $57\% \pm 5\%$; median survival was not reached. In contrast, it also indicates that outcome following autologous HSCT was poor—the LFS rate was $26\% \pm 5\%$ at 5 years, and median survival was 12 months. The low RI observed after allogeneic HSCT ($22\% \pm 5\%$), in contrast to the high RI after autologous HSCT ($70\% \pm 6\%$), suggests the existence of a graft-versus-leukemia effect following allogeneic transplantation. Results with autologous transplantation were, in fact, not different from those of conventional chemotherapy alone, which showed median survival from 4 to 14 months.^{8,10-15}

EL is a rare disease. This study is the only one giving actual information on HSCT in a large series of patients with EL. The low incidence of EL is indicated in the acute leukemia EBMT registry, in which only 559 (2.9%) patients with EL are registered for 19 513 patients with de novo AML (M. L., unpublished data, December 2000). Therefore, outside the registry, it is difficult to obtain sufficient data to study EL. The identification of patients with EL in prospective studies of HSCT for de novo AML, when FAB subtype description is mentioned, confirms that EL represents a small proportion of patients—1.6% to 3%—of all patients included in the studies.^{16,19,23,24} In details it corresponds in the MRC study with 12 EL patients out of 381 patients (6 EL patients underwent autologous HSCT and 6 chemotherapy alone),¹⁶ and it corresponds in the EORTC study with 6 EL patients out of 362 patients (2 underwent chemotherapy, 2 autologous HSCT, and 2 allogeneic HSCT).¹⁹ In

the Catalan study 5 EL patients out of 159 patients were randomized between autologous and allogeneic HSCT,²³ and in the Goelam study 9 EL patients out of 517 patients were included.²⁴

Data indicating the specific outcome of EL following allogeneic or autologous HSCT are scarce. In 1994, a Japanese group²⁵ reported as a single case a 2-year-old girl who had a survival up to 2 years at the time of publication after allogeneic bone marrow transplantation (BMT). More recently, the outcome of 27 patients with EL following allogeneic or autologous BMT was reported by the Royal Marsden group.²⁶ Nineteen patients had de novo EL: 5 could not receive BMT, 1 received autologous BMT, 9 sibling allogeneic BMT, 2 mismatch allogeneic BMT, and 2 matched unrelated BMT. For these 19 patients with de novo EL, the overall survival was 66% at 2 years; it was 53% in adults.

The results for the 104 allografted patients of our series matched those of most prospective trials of allogeneic HSCT for de novo AML in CR1 using an HLA identical family donor: LFS was 48% at 5 years in the Goelam study,²⁴ 43% at 4 years in the EORTC study,¹⁹ 43% at 4 years in the US intergroup study,²⁷ and 66% at 3 years in the BGMT study¹⁸; the Dutch study indicated an overall survival of 66% at 3 years.²⁸

Results of autologous HSCT in the present study were low. LFS at 5 years was 26%. This low LFS was attributed mainly to a high RI of 70% at 5 years. These results compared unfavorably with the data in the literature for de novo AML. Prospective comparative studies, including those mentioned above, have shown LFS of 54% at 5 years in the MRC AML 10 trial,¹⁶ 44% at 4 years in the Goelam study,²⁴ 48% at 5 years in the EORTC study,¹⁹ 51% at 3 years in the BGMT study¹⁸ and 67% at 4 years in the Catalan study.²³ Results of the present series were worse than those of the US intergroup study²⁷ and the Dutch study,²⁸ which reported the lowest LFS rates of all prospective comparative studies: 35% at 5 years and 37% at 3 years, respectively. However, the LFS of 26% for autografted EL patients in the present study concerns a mixture of all cytogenetics groups. The number of patients with informative karyotype in each group was too small, and we could not exclude that patients with favorable karyotype had better outcomes.

Results with autologous HSCT in this series look similar to those observed with autologous HSCT for myelodysplastic syndrome (MDS). A retrospective EBMT study²⁹ analyzed 55 patients with MDS or secondary AML; these patients underwent autologous BMT in first CR; LFS was 28% and RI was 69% at 2 years. This observation supports the hypothesis that primary MDS and EL are closely related disorders.¹⁵ Indeed, studies showed that EL is a trilineage disease^{8,9,15,30} similar to MDS. In fact, allogeneic HSCT is currently the only curative treatment for MDS, with reported LFS from 35% to 56%.³¹⁻³⁸ In younger patients (younger than 40) with low-risk MDS, long-term LFS was as high as 75%.³⁹

Prognostic factors found in this study were not different from those observed in HSCT for de novo AML (ie, age and GVHD). For autologous HSCT, a trend for a lower TRM was observed with peripheral blood; the absence of expected improvement of LFS was probably related to the small size of the population studied. However, in a previous EBMT study of 1393 patients who received autografts for AML in CR and comparing autologous blood cell to bone marrow transplantation, there was no difference on LFS and RI between blood cell transplantation and unpurged BMT.⁴⁰ For allogeneic HSCT, acute GVHD and age were the main prognostic factors identified in the present study; these factors are commonly found in allogeneic HSCT for de novo AML.

Unfortunately, informative cytogenetics with karyotype description was available for only 79 of 207 (38%) of the patients. Therefore, no prognostic evaluation of chromosomal abnormalities

was possible, and outcome analysis according to the SWOG cytogenetics prognostic groups was not performed. Results were known for 79 patients; 52 patients showed no chromosomal abnormality, and 27 patients showed clonal acquired abnormalities. For these 27 patients the abnormalities were heterogeneous. This is consistent with previous studies in which no specific pattern was found. In our series, involvement of chromosomes 5 or 7 was observed in 6 patients; these abnormalities were also found in other series of patients with EL^{9,15,26,30,41} and were associated with poor prognosis.¹⁵ Trisomy 8 was observed in 6 patients and reported in previous series of patients with EL.^{9,15,30} These abnormalities on chromosomes 5, 7, and 8 are also described in MDS.⁴²

We conclude that patients with EL who achieve CR1 should proceed to HLA matched allogeneic HSCT if a family donor is available. Allogeneic HSCT remains the treatment of choice to cure this rare and severe disease. In the absence of a family donor, autologous HSCT may cure a subset of patients, albeit at a lower proportion. There is little information on the value of unrelated allogeneic transplantation in EL.

Acknowledgments

We thank the following EBMT centers for registering patients with erythroleukemia analyzed in the study:

Abecasis, Manuel, Inst. Portugues Oncologia, Lisboa, Portugal; Alessandrino, E. Paolo, Policlinico San Matteo, Pavia, Italy; Amadori, Sergio, St Eugenio Hospital, Rome, Italy; Attal, Michel, Hopital de Purpan, Toulouse, France; Bacigalupo, Andrea, Ospedale San Martino, Genova, Italy; Barbui, Tiziano, Ospedale Bergamo, Bergamo, Italy; Beelen, Dietrich, University of Saarland, Homburg, Germany; Benedetti, Fabio, Policlinico Borgo Roma Ematologia, Verona, Italy; Bergmann, L., Universität Ulm, Germany; Blaise, Didier, Institut Paoli Calmettes, Marseille, France; Boasson, Marc, CHRU, Angers, France; Boogaerts, Marc A., University Hospital Gasthuisberg, Leuven, Belgium; Bosi, Alberto, Ospedale di Careggi, Firenze, Italy; Bron, Dominique, Institut Jules Bordet, Brussels, Belgium; Cahn, Jean-Yves, Hopital Jean Minjoz, Besancon Cedex, France; Chapuis, B., Hopital Cantonal Universitaire, Geneva, Switzerland; Clark, R. E., Royal Liverpool University Hospital, Liverpool, United Kingdom; Cordonnier, Catherine, Hôpital Henri Mondor, Creteil, France; Cornelissen, J. J., Daniel den Hoed Cancer Centre (AZR), Rotterdam, The Netherlands; Coser, Paolo, Hospital San Maurizio, Bolzano, Italy; Davies, John M., Western General Hospital, Edinburgh, Scotland, United Kingdom; De Souza, Carmino, Univ. Est. de Campinas, Campinas -SP, Brazil; Degos, Laurent, Hôpital St Louis, Paris, France; Evensen, Stein A., Rikshospitalet, Oslo, Norway; Falda, Michele, Azienda Ospedaliera S. Giovanni, Turin, Italy; Fanin, Renato, Udine University Hospital, Udine, Italy; Fassas, Athanasios, The George Papanicolaou General Hospital, Exokhi, Greece; Fasth, Anders, Queen Silvia Children's Hospital, Goeteborg, Sweden; Fauser, A. A., Klinik für Knochenmarktransplantation, Idar-Oberstein, Germany; Fernández-Ranada, José M., Hospital de la Princesa, Madrid, Spain; Ferrant, Augustin, Cliniques Universitaires St Luc, Brussels, Belgium; Fischer, Alain, Hôpital Necker, Paris, France; Franklin, Ian, Glasgow Royal Infirmary, Glasgow, Scotland, United Kingdom; García-Conde, Javier, Hospital Clínico Universitario, Valencia, Spain; Giustolisi, Rosario, Ferrarotto Hospital, Catania, Italy; Gluckman, Eliane, Hopital St Louis, Paris, France; Goldman, John M., Hammersmith Hospital, London, United Kingdom; Goldstone, Antony H., University College Lon-

don Hospital, London, United Kingdom; Gorin, Norbert C., Hopital Saint Antoine, Paris, France; Gratecos, Nicole, Hôpital de l'ARCHET I, Nice, France; Gratwohl, Alois, Kantonsspital, Basel, Switzerland; Greco, Michele Mario, Hospital Casa Sollievo Della Sofferenza, San Giovanni Rotondo, Italy; Greinix, Hildegard T., AKH Vienna, Vienna, Austria

Guilhot, F., Hopital La Miletrie, Poitiers, France; Hansz, J. K., Marcinkowski University, Poznan, Poland; Harhalakis, Nicholas, Evangelismos Hospital, Athens, Greece; Harousseau, Milpied, Hotel Dieu, Nantes, France; Hellmann, Andrzej, Medical University of Gdansk, Poland; Herrmann, R. P., Royal Perth Hospital, Western Australia, Australia; Hertenstein, Bernd, Medical School of Hannover, Germany; Holowiecki, J., Silesian Medical Academy, Katowice, Poland; Iacopino, Pasquale, Azienda Ospedaliera Bianchi-Melacrino-Morelli, Reggio Calabria, Italy; Iriando, A., Hospital Universitario 'Marqués de Valdecilla', Santander, Spain; Izzi, Teodosio, Spedali Civili, Brescia, Italy; Jacobsen, Niels, Rigshospitalet, Copenhagen, Denmark; Jouet, J. P., Hopital Claude Huriez, Lille Cedex, France; Kanz, L., Medizinische Klinik, Tübingen, Germany; Karianakis, G., Diagnostic & Therapeutic Center of Athens, Greece; Koc, Haluk, Ibni Sina Hospital, Ankara, Turkey; Labar, Boris, University Hospital Centre, Rebro, Zagreb, Croatia; Lambertenghi Delilieri, G., Ospedale Maggiore di Milano, Milan, Italy; Lasa Isasti, Ramon, Hospital Aranzazu, San Sebastian, Spain; Leblond, Veronique, Hôpital la Pitie-Salpetriere, Paris, France; Lenhoff, Stig, University Hospital, Lund, Sweden; Leone, Giuseppe, Università Cattolica S. Cuore, Rome, Italy; Littlewood, Tim, The Oxford Radcliffe Hospital, Oxford, United Kingdom; Ljungman, Per, Huddinge University Hospital, Sweden; Lucarelli, G., Pesaro Hospital, Pesaro, Italy; Mandelli, Franco, Università "La Sapienza," Rome, Italy; Marcus, Robert, Addenbrookes Hospital, Cambridge, United Kingdom; Martelli, Massimo F., Policlinico Monteluca, Perugia, Italy; McCann, Shaun, St James Hospital Trinity College, Dublin, Ireland; Michallet, Mauricette, Hopital E. Herriot, Lyons, France; Monserrat, Emilio, Hospital Clinic, Barcelona, Spain; Morris, T. C. M., Belfast City Hospital, Belfast, Northern Ireland, United Kingdom; Mufti, G. J., King's College School of Medicine, London, United Kingdom; Niederwieser, Dietger, University of Leipzig, Germany; Noens, L. A., University Hospital Ghent, Belgium; Novitzky, Nicolas, UCT Medical School, Cape Town, South Africa; Ossenkoppele, G. J., Free University Hospital Amsterdam, The Netherlands; Pico, José Luis, Institut Gustave Roussy, Villejuif Cedex, France; Pogliani, Enrico Maria, Ospedale S. Gerardo, Monza, Italy; Powles, Ray, Royal Marsden Hospital, Sutton, Surrey, United Kingdom; Prentice, H. G., Royal Free Hospital, London, United Kingdom; Proctor, S. J., Royal Victoria Infirmary, Newcastle upon Tyne, United Kingdom; Reiffers, J., Hopital du Haut Leveque, Pessac, France; Remes, Kari, Turku University Central Hospital, Turku, Finland; Rio, Bernard, Hotel Dieu, Paris, France; Rizzoli, Vittorio, University of Parma, Italy; Rodeghiero, Francesco, S. Bortolo Hospital, Vicenza, Italy; Rodríguez Fernández, Juan M., Hospital 'Virgen del Rocío', Sevilla, Spain; Rossi, Jean Francois, University Hospital, Montpellier, France; Rotoli, Bruno, Federico II Medical School, Napoli, Italy; Russell, N. H., Nottingham City Hospital, Nottingham, United Kingdom; Ruutu, Tapani, Helsinki University Central Hospital, Helsinki, Finland; Sanz, Miguel A., Hospital Universitario La Fe, Valencia, Spain; Schaefer, U. W., University Hospital, Essen, Germany; Schanz, Urs, University Hospital, Zurich, Switzerland; Schattenberg, A., Nijmegen University Medical Center, The Netherlands; Schey, S. A. M., Guy's Hospital, London, United Kingdom; Schmitz, Norbert, Christian-Albrechts-University, Kiel,

Germany; Schots, R., University Hospital VUB, Brussels, Belgium; Schroyens, W., Universiteit Antwerpen (UZA), Antwerp, Edegem, Belgium; Scimè, Rosanna, Ospedale V. Cervello, Palermo, Italy; Selleslag, D., A. Z. Sint-Jan, Bruges, Belgium; Sierra, Jorge, Hospital Santa Creu i Sant Pau, Barcelona, Spain; Simonsson, Bengt, University Hospital, Uppsala, Sweden; Slavin, Shimon, Hadassah University Hospital, Jerusalem, Israel; Tura, Sante, Hospital San Orsola, Bologna, Italy; Van den Berg, H., Academic

Medical Centre van Amsterdam, The Netherlands; van Marwijk Kooy, M., Isala Klinicken Zwolle, The Netherlands; Verdonck, Leo F., University Medical Centre, Utrecht, The Netherlands; Vitek, Antonin, Institute of Hematology and Blood Transfusion, Prague, Czech Republic; Volpe, Ettore, Ematologia 'Giovanni di Guglielmo', Avellino, Italy; Wahlin, Anders, Umea University Hospital, Sweden; Wandt, Hannes, Klinikum Nürnberg, Nuremberg, Germany; Zander, Axel R., University Hospital Eppendorf, Hamburg, Germany.

References

- Copelli M. Di una emopatia sistemizzata rappresentata da una imperplasia eritroblastica (eritronatosi). *Pathologica*. 1912;4:460.
- Di Guglielmo G. Ricerche di ematologia, I: un caso di erythro-leucemia. *Folia Med*. 1917;3:386.
- Moeschlin S. Erythroblastosen, erythroleukamien und erythroblastamien. *Folia Haematol (Leipzig)*. 1940;64:262.
- Dameshek W. The Di Guglielmo's syndrome. *Blood*. 1958;13:192.
- Dameshek W, Gunz F. *Leukemia*. New York, NY: Grune & Stratton; 1964.
- Bennet JM, Catovsky D, Daniel MT, et al. Proposals for the classification of the acute leukaemias. *Br J Haematol*. 1976;33:451.
- Bennet JM, Catovsky D, Daniel MT, et al. Proposed revised criteria for the classification of acute myeloid leukemia. *Ann Intern Med*. 1985;103:626-629.
- Roggli VL, Saleem A. Erythroleukemia: a study of 15 cases and literature review. *Cancer*. 1982;49:101-108.
- Atkinson H, Hrisinko MA, Weil SC. Erythroleukemia: a review of 15 cases meeting 1985 FAB criteria and survey of the literature. *Blood Rev*. 1993;6:204-214.
- Schwartz AD, Zelson JH, Pearson HA. Acute myelogenous leukemia with compensatory but ineffective erythropoiesis: diGuglielmo's syndrome. *J Pediatr*. 1970;77:653-657.
- Bloomfield CD, Brunning RD, Kennedy BJ. Daunorubicin-prednisone treatment of erythropoiesis. *Ann Intern Med*. 1974;81:746-750.
- Hetzel P, Gee TS. A new observation in the clinical spectrums of erythroleukemia: a report of 46 cases. *Am J Med*. 1978;64:765-772.
- Roggli VL, Subach J, Saleem A. Prognostic factors and treatment effects on survival in erythroleukemia: a retrospective study of 134 cases. *Cancer*. 1981;48:1101-1105.
- Frydecka I, Brodzka W, Lawinska B, Sciborski R. Clinical course and results of treatment of erythroleukemia. *Folia Haematol*. 1984;111:283-289.
- Olopade OI, Thangavelu M, Larson RA, et al. Clinical, morphological and cytogenetic characteristics of 26 patients with acute erythroblast leukemia. *Blood*. 1992;80:2873-2882.
- Burnett AK, Goldstone AH, Stevens RMF, 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. *Lancet*. 1998;351:700-708.
- Slovack ML, Kopecky LJ, Cassileth PA, et al. Karyotype analysis predicts outcome of preremission and postremission therapy in adult acute myeloid leukemia: a Southwest Oncology Group/Eastern Cooperative Oncology Group Study. *Blood*. 2000;96:4075-4083.
- Reiffers J, Stoppa AM, Attal M, et al. Allogeneic vs autologous stem cell transplantation vs chemotherapy in patients with acute myeloid leukemia in first remission: the BGMT 87 study. *Leukemia*. 1996;10:1874-1882.
- Zittoun RA, Mandelli F, Willemze R, et al. Autologous or allogeneic bone marrow transplantation compared with intensive chemotherapy in acute myelogenous leukemia. *N Engl J Med*. 1995;332:217-223.
- Gorin NC. Autologous stem cell transplantation in acute myelocytic leukemia: a review. *Blood*. 1998;92:1073-1090.
- Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1957;53:457-481.
- Cox DR. Regression models and life tables. *J R Stat Soc B*. 1972;34:187-220.
- Sierra J, Brunet S, Granena A, et al. Feasibility and results of bone marrow transplantation after remission induction and intensification chemotherapy in de novo acute myeloid leukemia. *J Clin Oncol*. 1996;14:1353-1363.
- Harrousseau JL, Cahn JY, Pignon B, et al. Comparison of autologous bone marrow transplantation and intensive chemotherapy as postremission therapy in adult acute myeloid leukemia. *Blood*. 1997;90:2978-2986.
- Kogawa K, Sekine I, Masuda T, et al. Bone marrow transplantation for erythroleukemia: a case report. *Acta Paediatr Jpn*. 1994;36:693-696.
- Killick S, Matutes E, Powles RL, et al. Acute erythroid leukemia (M6): outcome of bone marrow transplantation. *Leuk Lymphoma*. 1999;35:99-107.
- Cassileth PA, Harrington DP, Appelbaum FR, et al. Chemotherapy compared with autologous or allogeneic bone marrow transplantation in the management of acute myeloid leukemia in first remission. *N Engl J Med*. 1998;339:1649-1656.
- Löwenberg B, Verdonck LJ, Dekker AW, et al. Autologous bone marrow transplantation in acute myeloid leukemia in first remission: results of a Dutch prospective study. *J Clin Oncol*. 1990;8:287-294.
- De Witte T, van Biezen A, Hermans J, et al. Autologous bone marrow transplantation for patients with myelodysplastic syndrome (MDS) or acute myeloid leukemia following MDS. *Blood*. 1997;90:3853-3857.
- Cuneo A, Orshoven AV, Michaux JL, et al. Morphological, immunological and cytogenetic studies in erythroleukemia: evidence for multilineage involvement and identification of two distinct cytogenetic-clinicopathological types. *Br J Haematol*. 1990;75:346-354.
- Anderson JE, Appelbaum FR, Fisher LD, et al. Allogeneic bone marrow transplantation for 93 patients with myelodysplastic syndrome. *Blood*. 1993;82:677-681.
- Anderson JE, Appelbaum FR, Storb R. An update on allogeneic marrow transplantation for myelodysplastic syndrome. *Leuk Lymphoma*. 1995;17:95-99.
- Ratanaatharathorn V, Karanes C, Uberti J, et al. Busulfan-based regimens and allogeneic bone marrow transplantation in patients with myelodysplastic syndromes. *Blood*. 1993;81:2194-2199.
- Nevill TJ, Shepherd JD, Reece DE, et al. Treatment of myelodysplastic syndrome with busulfan-cyclophosphamide conditioning followed by allogeneic BMT. *Bone Marrow Transplant*. 1992;10:445-450.
- Sutton L, Leblond V, Le Maignan C, et al. Bone marrow transplantation for myelodysplastic syndrome and secondary leukemia: outcome of 86 patients. *Bone Marrow Transplant*. 1991;7:39.
- De Witte T, Zwaan F, Hermans J, et al. Allogeneic bone marrow transplantation for secondary leukaemia and myelodysplastic syndrome: a survey by the Leukaemia Working Party of the European Bone Marrow Transplantation Group (EBMTG). *Br J Haematol*. 1990;74:151-155.
- Longmore G, Guinan E, Weinstein JH, et al. Bone marrow transplantation for myelodysplasia and secondary acute non-lymphoblastic leukemia. *J Clin Oncol*. 1990;8:1707-1714.
- O'Donnel MR, Nademanee AP, Snyder DS, et al. Bone marrow transplantation for myelodysplastic and myeloproliferative syndrome. *J Clin Oncol*. 1987;5:1822-1826.
- Heaney ML, Golde DW. Myelodysplasia. *N Engl J Med*. 1999;340:1649-1660.
- Reiffers J, Labopin M, Sanz M, et al. Autologous blood cell vs marrow transplantation for acute myeloid leukemia in complete remission: an EBMT study. *Bone Marrow Transplant*. 2000;25:1115-1119.
- Kadamn PR, Balsara BR, Zafarullah KZ, Dadabhoy KD, Bhisey AN, Advani SSH. Cytogenetic features of erythroleukemia (EL): a study of 11 cases. *Cancer Genet Cytogenet*. 1990;50:89-96.
- Heim S, Mitelman F. *Acute myeloid leukemia*. In: *Cancer Cytogenetics*. 2nd ed. New York, NY: Wiley-Liss; 1995:69-140.