Treatment reduction in highly selected standard-risk childhood acute lymphoblastic leukemia. The AIEOP ALL-9501 study

Maurizio Aricò
Valentino Conter
Maria Grazia Valsecchi
Carmelo Rizzari
Marie France Pinta Boccalatte
Elena Barisone
Chiara Messina
Giulio De Rossi
Luca Lo Nigro
Andrea Pession
Franco Locatelli
Concetta Micalizzi
Giuseppe Basso
Giuseppe Masera
for the Associazione Italiana di Ematologia ed Oncologia Pediatrica (AIEOP)

Background and Objectives. Treatment of childhood standard-risk (SR) acute lymphoblastic leukemia (ALL) is generally successful. However, intensive chemotherapy regimens may be associated with severe treatment sequelae. Efforts are therefore being made to identify those patients in whom less intensive treatment would be equally successful but cause fewer long-term sequelae. The aim of this study was to evaluate the efficacy of treatment reduction in a subset of children with ALL at minimal risk of failure.

Design and Methods. The population of patients with SR ALL included children aged between 1 and 6 years with less than 20,000 WBC/mm^3, non-T immunophenotype, DNA index between 1.16 and 1.6, absence of t(9;22) and t(4;11) clonal translocations, no extramedullary leukemia, good response to prednisone and complete remission (CR) at the end of induction therapy. A reduced-intensity, BFM-type treatment schedule (AIEOP-ALL 9501 protocol) was used. Induction therapy was based on vincristine, prednisone, L-asparaginase and intrathecal methotrexate only; high-dose-methotrexate (2 g/m^2) was given ×4. The BFM Protocol II was given as reinduction therapy; thus the total dose of anthracyclines was 120 mg/m^2 and no epipodophyllotoxins or cranial irradiation were employed.

Results. Between May 1995 and December 1999, 123 patients were identified as having SR-ALL (7.8% of the ALL-95 population), of whom 102 received the SR protocol. After a median follow-up of 5.9 years, 11 patients in the SR protocol had relapsed, 1 had died in remission, and 1 had developed a second malignant neoplasm. The probabilities (standard errors) of survival and event-free survival (EFS) were, respectively, 97.0% (1.7) and 86.7% (3.5) at 5 years, and 95.3% (2.4) and 86.7% (3.5) at 7 years.

Interpretations and Conclusions. Although most of the relapsed patients were rescued, the long-term EFS probability in this small, highly selected group of patients remains inferior to expectation. Thus, alternative selection criteria, such as treatment response measured by minimal residual disease, should be considered to address the issue of treatment reduction.

Key words: treatment reduction, childhhod, ALL, DNA index.

Haematologica 2005; 90:1186-1191

Correspondence:
Maurizio Aricò, Oncoematologia Pediatrica, Ospedale dei Bambini "G. Di Cristina", Via Benedettini 1 90134 Palermo, Italy.
E-mail: arico@ospedalecivicopa.org

From the Oncoematologia Pediatrica, Ospedale dei Bambini G.Di Cristina, Palermo (MA); Clinica Pediatrica, Università Milano Bicocca, Osp.San Gerardo, Monza (VC, CR, GM); Medical Statistics Unit, University of Milano-Bicocca (MGV); S.C. Ematologia Oncologia, A.O. Pediatrica Santobono Pausilipon, Napoli (MFPB); Dip. Scienze Pediatriche, OIRM, Torino (EB); Catt. Oncoematologia Pediatrica, Università, Padova (CM, GB); Div. Ematologia Pediatrica, IRCCS Ospedale Bambin Gesù, Roma (GDR); Div. Ematologia-Oncologia Pediatrica, Clinica Pediatrica Università, Catania (LLN); Oncoematologia Pediatrica, Policlinico S.Orsola-Malpighi, Bologna (AP); Oncoematologia Pediatrica, IRCCS, Policlinico San Matteo, Pavia (FL); Ematologia Oncologia Pediatrica, IRCCS G.Gaslini, Genova (CM), Italy.

Acute lymphoblastic leukemia (ALL), the most common type of cancer in children, is highly responsive to chemotherapy with around 80% of patients being expected to survive with current chemotherapy regimens. Such favorable results have been achieved by several co-operative groups and large single institutions worldwide.[1-8] Since 1988, the *Associazione Italiana Ematologia Oncologia Pediatrica* (AIEOP) has adopted a risk-directed treatment strategy, which was initially derived from the German BFM study group experience[2] and then developed through a close inter-group co-operation in the frame of the International BFM Study Group (I-BFM-SG).[9-11] Further improvement of treatment results for children with standard risk ALL may be difficult to achieve. On the other hand, the improved outcome achieved worldwide mostly by use of intensive chemotherapy regimens may be associated with treatment sequelae, such as cardiac failure or secondary neoplasms.[12-18]

For this reason, investigators in most co-operative study groups and large institutions have been challenged to refine their selection criteria for standard-risk ALL, in order to identify a subgroup of patients for whom long-term event-free-survival (EFS) greater than 90% may be achieved using a treatment associated with a limited potential for long-term sequelae. Criteria used to identify lower-risk patients have included age (non-infant, non-adolescent) and female gender, low tumor burden (measured as leukocyte count with or without correction for hepato-splenomegaly),[19] biological markers such as ploidy,[20-22] absence or presence of specific chromosomal translocations, and favorable early

response to therapy, defined as blast count either in peripheral blood on day 8 or in marrow on day 15. As for most other prognostic factors, those directed at defining patients at low risk of leukemia relapse are also largely dependent on the type of treatment used, and thus may not be universally reproduced.

Between 1988 and 1991, the AIEOP conducted the ALL-88 study, in which standard-risk ALL was mainly identified by low tumor burden, according to the so-called BFM risk factor, based on leukocyte count, liver and spleen size.[2] This group, accounting for 20.5% of all patients, was treated with a BFM-type chemotherapy backbone,[2] i.e full induction (protocol I), consolidation with high-dose methotrexate (5 g/m^2), and less intensive reinduction therapy (protocol III instead of protocol II), without cranial radiation or extended intrathecal methotrexate during continuation therapy. This group had a 7-year EFS of 80.0% (SE 4.5) and a cumulative incidence of isolated central nervous system (CNS) relapse of 6.5% (SE, 2.8).

In the following childhood ALL study of the International BFM Study group, in the arm for standard-risk patients, denominated IDH-ALL-91 and conducted in three countries (Italy, the Netherlands, and Hungary), the children treated with reduced BFM-type chemotherapy were randomized to extended high-dose L-asparaginase.[23] Inclusion criteria were: age 1-15 years, non-T-lineage ALL, low tumor burden (defined as BFM risk factor lower than 0.8), and good response to prednisone. Treatment consisted of BFM-type modified chemotherapy: 4-drug induction (protocol IA only, omitting the B part); consolidation with four courses of high-dose methotrexate, 2 g/m^2; reinduction with modified protocol II (only two doses of anthracyclines); at the beginning of continuation therapy, (6-methylprednisolone, methotrexate, and triple intrathecal chemotherapy), patients were randomized to receive or not 20 weekly high doses (25,000 IU/m^2) of L-asparaginase. For the AIEOP, the 7-year EFS probability in the standard-risk group, accounting for 24.3% of all the patients with ALL, was 81.8% (SE 2.4).

In May 1995, the AIEOP started the standard-risk arm of the ALL-95 study, denominated 95-01, aimed at selecting a small subset of patients at minimal risk of treatment failure – identified not only by early response *in vivo*, one of the strongest predictors in the I-BFM-SG experience,[2,24] but also by age, blood count and, in particular, by high DNA content, according to previous experience reported by the Pediatric Oncology Group[25,26] – to be treated with a reduced-intensity, BFM-type schedule. The aim of this study was to achieve a long-term EFS compatible with the 90% outcome reported by the Pediatric Oncology Group.[27]

Design and Methods

Study population

Eligibility criteria for standard-risk ALL included all of the following: age 1 to less than 6 years; non-T-ALL; white cell count less than 20,000 /mm^3; DNA index between 1.16 and 1.6; absence of t(9;22) and t(4;11) clonal translocations; no extramedullary leukemia; prednisone good response (less than 1,000 blasts/mm^3 in peripheral blood after 7 days of steroids and one injection of intrathecal methotrexate).[19] Patients who failed to achieve complete remission by day 43 were shifted to the high-risk group. Written informed consent to treatment was obtained in all cases from the patients' legal guardians.

Diagnostic studies

Confirmation of the diagnosis as well as immunophenotype, DNA index, and t(9;22) and t(4;11) clonal translocations, were investigated at the AIEOP reference laboratory (G.B., Padua, Italy). Cytogenetic analysis was not systematically performed.

Treatment protocol

Treatment consisted of a modified BFM schedule. In detail, after 7 days of pre-phase with steroids and one injection of intrathecal methotrexate, all patients received a three-drug induction regimen (43-day vincristine, prednisone, Erwinia asparaginase) alsting 43 days; the usual second part of the BFM induction (protocol IB) was omitted. Consolidation therapy included four courses of high-dose methotrexate (2 g/m^2). Reinduction therapy consisted of protocol II. Continuation therapy consisted of oral 6-mercaptopurine (50 mg/m^2 daily), methotrexate (20 mg/m^2 i.m. weekly) and extended triple intrathecal chemotherapy, for a total treatment duration of 24 months (Table 1). Supportive care was given according to each group's current policy. In December 1999, on the basis of the observation that treating physicians expressed a low confidence in treatment reduction, this 95-01 standard-risk protocol was closed; thereafter, standard-risk patients were treated in the same way as the intermediate-risk group with a full BFM chemotherapy regimen, until the end of August 2000.

Definitions

Complete remission was defined as no physical signs of leukemia, no detectable leukemic cells on blood smears, bone marrow with active hematopoiesis and less than 5% identifiable leukemic blast cells, and normal (≤ 5 leukemic blast cells/mm^3) cerebro-spinal fluid. A bone marrow aspirate taken on day 43 was examined for the evaluation of remission status.

Table 1. Treatment schedule for standard-risk childhood ALL in the AIEOP-ALL-95-01 study.

Protocol phase/drug	*mg/m²*	*Day*
Induction		
Vincristine	1.5 (≤2.5 mg)	8, 15, 22, 29
Prednisone	60	1-28°
L-Asparaginase	10,000°°	19,22,25,28,31,34,37,40
Methotrexate it	by age*	1
Triple i.t.*	by age*	15,29
Consolidation		
Methotrexate i.v.	2,000	8,22,36,50
Leucovorin (levo)	7.5	42,48#
Triple intrathecal *	by age*	8,22,36,50
6-mercaptopurine	25	1-56
Reinduction		
Dexamethasone	10	1-21°
Vincristine	1.5 (≤2.5 mg)	8,15,22,29
Adriamycin	30	8,15,22,29
L-Asparaginase	10,000°°	8,11,15,18
6-thioguanine	60	36-49
Cyclophosphamide	1,000	36
Cytarabine	75	38-41,45-48
Triple i.t.*	by age*	38,45
Continuation		
6-mercaptopurine	50	Daily
Methotrexate i.m.	20	Weekly
Triple i.t.*	by age*	q 8 weeks (≤9 times)

*°Then tapered; *age-adjusted doses of triple intrathecal therapy for methotrexate, cytarabine and prednisolone were, respectively, as follows: <1 year 6/16/4 mg; ≥1< 2 years 8/20/6 mg; ≥2< 3 years 10/26/8 mg, > 3 years 12/30/10 mg; #hours after methotrexate infusion start; °°(IU/m²).*

Table 2. Outcome of 102 patients with standard-risk childhood ALL enrolled in the AIEOP-ALL-9501 study.

	N (%)	*Time from diagnosis (years)*
A		
Total	102	
Relapse	11	Median: 2.7
Death in remission	1	0.5
Second malignant neoplasm	1	4.8 years
Continuous complete remission	89	Median: 5.6

B *Characteristics of the 11 patients with standard-risk childhood ALL enrolled in the AIEOP-ALL-9501 study who relapsed*

Case #	*Age at diagnosis (months)*	*Sex*	*WBC count/ mm³*	*Immune phenotype*	*DNA index*	*BM day 15*	*Site and time of relapse (years)*
1	23	F	2,500	Pre-B	1.22	M2	Bone marrow, 2.0
2	58	F	1,630	Pre-B	1.24	M1	Bone marrow, 2.5
3	59	F	11,580	Common	1.28	M3	Bone marrow, 2.6
4	29	M	2,990	Pre-B	1.16	M1	Bone marrow, 2.6
5	71	F	7,800	Pre-B	1.24	M2	Bone marrow, 3.0
6	49	M	3,800	Common	1.23	M2	Bone marrow, 3.6
7	39	F	10,500	Common	1.24	M3	Bone marrow, 3.8
8	36	F	1,400	Common	1.24	M1	Bone marrow, 3.8
9	43	M	5,800	Pre-B	1.17	M3	Central nervous system, 1.2
10	50	M	4,970	Common	1.21	M1	Marrow+Testis, 3.0
11	55	F	12,990	Pre-B	1.33	M1	Eye, 2.7

Statistical analysis

EFS and survival curves were estimated according to the Kaplan-Meier method[28] and pointwise 95% confidence intervals were calculated based on the Greenwood estimate of the standard error. The starting point for the observation time was the date of diagnosis. For EFS, death in induction, relapse, death in continuous complete remission, or secondary malignancy were counted as events. Death from any cause was considered an event in estimating the probability of survival. The observation time was censored at the last follow-up date if no event was observed or if the patient had been lost to follow-up. Follow-up was updated at December 31st, 2003, and the series had a median follow-up of 5.9 years (one patient was lost to follow-up).

The Cox regression model was applied to estimate treatment effects adjusting for known prognostic variables (white cell count, with a cut-off at 10,000/mm³; gender; age in years; and bone marrow blasts day 14, <5% vs ≥5%). Before applying the Cox model, the presence of major departures from the proportional hazards assumptions was excluded by graphical checks. The analyses were carried out with the SAS package (SAS Institute, Cary, NC, USA).

Results

Patients' characteristics

Between May 1995 and December 1999, 123 patients were identified as having standard-risk ALL (7.8% of the total ALL-95 population). Twenty-one patients fulfilling standard-risk criteria were nevertheless treated with the intermediate risk group regimen because of medical decisions: of these 21 patients, one had a marrow relapse at 16 months, while 20 remained in first remission. Of note, two patients who initially presented with standard-risk features failed to achieve complete remission by day 43 and were thus, by protocol, allocated to the high risk group. Of the 102 study patients, 72 had common ALL, 29 had pre-B-ALL and 1 had pre-pre-B (CD10 negative) ALL. Bone marrow examination on day 15 was performed in 98 cases, and 68, 19 and 11 had M1 (<5% blasts), M2 (<25% blasts) and M3 (≥25%) marrow, respectively. Of these 102 patients, one died in remission of septicemia 6 months after diagnosis, and one developed a second malignant neoplasm, which was a T-lineage ALL, 4.8 years after the diagnosis of the initial B-lineage ALL. Eleven patients relapsed at a median time of 32.4 months (range, 11.4-46.4 months), and their main characteris-

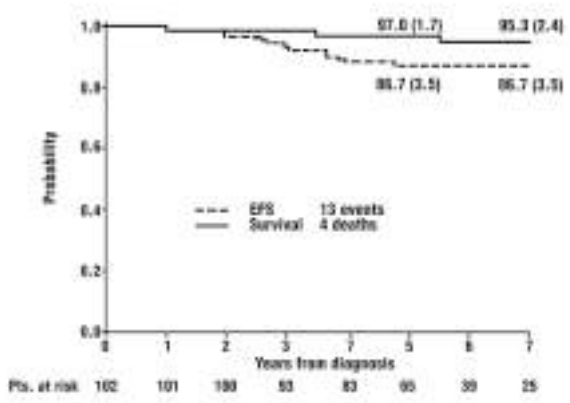

Figure 1. Event-free survival (SE) and survival of 102 children with standard-risk ALL, treated in the AIEOP-ALL-9501 study.

tics are summarized in Table 2. Second-line treatment included chemotherapy-only for three patients, of whom one subsequently died; eight patients were re-treated with chemotherapy followed by intensification with bone marrow transplantation, either autologous (n=2, both alive) or allogeneic from a matched (n=4, 3 alive) or partially matched (n=2, both alive) unrelated donor. The remaining 89 patients were still in first complete remission after a median follow-up of 5.6 years. The probabilities (95% confidence intervals) of survival and EFS were, respectively, 97.0% (93.7-100), and 86.7% (79.8-93.6) at 5 years and 95.3% (90.6-100.0) and 86.7% (79.8-93.6) at 7 years (Figure 1). There was no difference in the outcome (p value=0.89) between the 56 females [7 events, 5-year EFS 87.3% (78.5-96.1)] and the 46 males [6 events, 5-year EFS 85.9% (75.3-96.5)]. There was no significant difference in the outcome (p value=0.06) between the 68 patients with <5% blasts in day-15 marrow [6 events, 5-year EFS 90.9% (84.0-97.8)] and the 30 patients with M2-M3 day-15 marrow [7 events, 5-year EFS 75.5% (59.6-91.4)]. None of the variables white cell count, age, sex or percentage blasts in day-15 marrow had a prognostic significance in this standard-risk group when analyzed in a Cox regression model.

Discussion

This study was aimed at identifying a selected subpopulation of childhood ALL in whom a reduced-intensity BFM-type chemotherapy could be applied, with the purpose of obtaining a long-term EFS probability in the range of 90% with a minimal risk of late sequelae. On the basis of the experience gained by other groups,[20-22,24-29] we decided to select the children using hyperdiploidy – defined as DNA index comprised between 1.16 and 1.6 – in addition to the traditional parameters of age, leukocyte count, immunophenotype, and favorable response to steroids, defined as clearance of blasts in peripheral blood on day 8 (the so-called *good steroid response*). With these selection criteria, we identified a very small subgroup of patients, accounting for only 7.8% of the total ALL population.

The treatment applied did not include two elements that are considered among the most toxic ones: namely cranial irradiation, which was replaced by extended use of intrathecal triple chemotherapy,[30] and epipodophyllotoxins, a family of antileukemic agents that have been associated with an increased risk of promoting development of second malignancy, especially acute myeloid leukemia.[15,16] Furthermore, the long-term risk of anthracycline-associated cardiomyopathy, which is at least in part dose-dependent, was also reduced by using a cumulative dose of only 120 mg/m^2.[12-14]

Finally, deaths during induction (historically at a 1% level with conventional BFM induction),[29] could also have been avoided by reducing therapy.

The probability of EFS at 7 years of patients in this protocol was 86.7%, a result which could be considered not fully satisfactory in such a small, selected subpopulation of childhood ALL. Indeed, the 95% confidence interval indicates that EFS could be as good as 94% or as bad as 80% in this type of patient when treated less intensively than usually done in BFM-like protocols. A low confidence with the concept of treatment reduction was observed during the study, as 15% of the standard-risk patients had been shifted by treating physicians from the standard to the intermediate-risk protocol. This reflected the clinical feeling that disease control in the marrow was not satisfactory and prompted the steering committee to close recruitment in advance. Although no lesson can be drawn from the small subset of patients shifted to the intermediate risk group, they had an apparent, non-significant, slight advantage from more intensive therapy.

When evaluating these results, it remains to be considered that the most frequent cause of treatment failure was leukemia relapse, and that most of the relapsed patients could be rescued by second-line treatment, including chemotherapy and intensification with bone marrow transplantation in most cases, thus allowing a 95.3% probability of survival at 7 years.

In conclusion, the results of this study are not markedly inferior to those obtained by other groups that attempted treatment reduction. Nevertheless, for the future, a better outcome with results clearly above 90% should be the goal in a larger subgroup of

ALL patients. Indeed, in the current AIEOP-BFM-ALL-2000 study, in addition to the usual clinical criteria, we are using polymerase chain reaction-based determination of minimal residual disease to stratify patients with childhood ALL into three groups. In the standard-risk group, accounting for about 40% of the patients, the safety of a moderate treatment reduction during late intensification is being explored by means of randomization. Time will tell if and how far treatment reduction may be safely applied in a large proportion of cases of childhood ALL without compromising the treatment results achieved with contemporary, intensive chemotherapy regimens.

Appendix

Institutions which enrolled patients in the AIEOP-ALL-9501 study: Ancona, Clinica Pediatrica (Prof. G.V. Coppa, Dott. P. Pirani); Bari, Clinica Pediatrica I (Prof. F. Schettini, Dott. N. Santoro); Bari, Clinica Pediatrica II (Prof. N. Rigillo, Dott.ssa S. Bagnulo); Bergamo, Div. Pediatria (Dott. P.E. Cornelli), Ematologia (Prof. T. Barbui); Bologna, Clinica Pediatrica (Prof. G. Paolucci, Prof. A. Pession); Brescia, Clinica Pediatrica (Prof. A.G. Ugazio, Dott. A. Arrighini); Cagliari, Servizio Oncoematologia Pediatrica (Prof. P.F. Biddau, Dott.ssa R. Mura); Catania, Div. Oncoematologia Pediatrica (Prof. G. Schilirò, Dott. L. Lo Nigro); Catanzaro, Div. Ematologia (Prof. S. Magro, Dott.ssa C. Consarino); Firenze, Ospedale Meyer, Dip. Pediatria, U.O. Oncoematologia Pediatrica (Prof.ssa G. Bernini, Dott.ssa A. Lippi); Genova, Ist. "G.Gaslini" (Prof. P.G. Mori, Dott.ssa C. Micalizzi); Modena, Clinica Pediatrica (Prof. S. Bernasconi, Dott.ssa M. Cellini); Monza, Clinica Pediatrica (Prof. G. Masera, Dott. V. Conter); Napoli, Ospedale Pausilipon (Prof. V. Poggi, Dott.ssa M.F. Pintà Boccalatte); Napoli, II Università, Dip. Pediatria, Servizio Autonomo Oncologia Pediatrica (Prof.ssa M.T. Di Tullio, Prof.ssa F. Casale); Napoli, Ospedale SS Annunziata (Prof. F. Tancredi, Dott. A. Correra); Padova, Clinica Pediatrica II (Prof. L. Zanesco, Dott.ssa C. Messina); Palermo, Clinica Pediatrica I (Dott. M. Aricò, Dr. O. Ziino); Parma, Clinica Pediatrica (Dott. G. Izzi, Dott.ssa P. Bertolini); Pavia, Oncoematologia Pediatrica (Prof. F. Locatelli); Perugia, Div. Oncoematologia Pediatrica, Osp. Silvestrini (Dott. A. Amici, Dott. P. Zucchetti); Pescara, Div. Ematologia (Dott. Fioritoni, Dott. A. Di Marzio); Pisa, Clinica Pediatrica III (Prof. P. Macchia, Dott. C. Favre); Reggio Calabria, Div. Ematologia, Ospedali Riuniti (Prof. F. Nobile, Dott.ssa M. Comis); Roma, Div. Ematologia Pediatrica, Osp. "Bambin Gesù" (Prof. G. De Rossi, Dott. C. Baronci); Roma, Cattedra Ematologia (Prof. F. Mandelli, Dott.ssa A.M. Testi); San Giovanni Rotondo, Ospedale "Casa Sollievo della Sofferenza", Div. Pediatria, Sezione Ematologia ed Oncologia Pediatrica (Prof. P. Paolucci, Dott. S. Ladogana); Sassari, Clinica Pediatrica (Prof. D. Gallisai, Dott. C. Cosmi); Torino, Clinica Pediatrica (Prof. E. Madon, Dott.ssa E. Barisone); Trieste, Clinica Pediatrica (Prof. P. Tamaro, Dott. G.A. Zanazzo); Verona, Clinica Pediatrica (Prof. L. Tatò, Dott. P.L. Marradi). AIEOP data center: COFONOP, Clinica Pediatrica Università di Bologna (Prof. A. Pession, Dr. R. Rondelli) & CORS, Clinica Pediatrica, Università di Milano Bicocca (Prof. M.G. Valsecchi, Dr. D. Silvestri).

MA: study design, clinical monitoring of the study, data analysis, draft writing; VC: study design, clinical monitoring of the study, data analysis, draft writing; MGV: study design, data analysis, draft writing; CR: clinical monitoring of the study, data analysis; MFPB, EB, CM, GDR, LLN, AP: clinical monitoring of the study; FL, CM: clinical monitoring of the study, draft writing ; GB: responsible for the central AIEOP laboratory, draft writing; GM: study design, clinical monitoring of the study, data analysis, draft writing. The authors declare that they have no potential conflict of interest.

Partially supported by: Ricerca Corrente n. 2003/02/P/001132, Ministero della Salute, OPBG (GDR); Fondazione Città Della Speranza (GB, CM); MIUR, ex-40 and ex-60% (GB); CNR (GB); MIUR progetto "Caratterizzazione biologica e strategie terapeutiche innovative nelle malattie sistemiche dell'adulto e dell'età pediatrica" (GB).

We would like to thank Daniela Silvestri for her valuable contribution to the management and evaluation of this study.

Manuscript received February 23, 2005. Accepted June 29, 2005.

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