Acta Pædiatr Scand 70: 609–614, 1981

ACUTE LYMPHOBLASTIC LEUKEMIA IN SWEDISH CHILDREN 1973–1978

G. GUSTAFSSON, A. KREUGER and A. DOHLWITZ
for the Swedish Child Leukemia Group

From the Departments of Paediatrics, University Hospital, Uppsala and the County Hospital, Nyköping, Sweden

ABSTRACT. Gustafsson, G., Kreuger, A. and Dohlwitz, A. (Departments of Paediatrics, University Hospital, Uppsala, and County Hospital, Nyköping, Sweden). Acute lymphoblastic leukemia in Swedish children 1973–1978. Acta Paediatr Scand, 70: 609, 1981.—Three hundred and sixty-seven children with acute lymphoblastic leukemia have been diagnosed in Sweden 1973–1978, 345 of whom were treated according to the national uniform regimens of the Swedish Child Leukemia Group (SCLG). The patients were classified into an SR (standard risk) and an IR (increased risk) group. Remission was obtained in 354 patients (96 %). With 12–84 months observation time the total survival was 54 % and the diseasefree survival 44 %. A more intensive cytostatic regimen in the induction period increased considerably the diseasefree survival for the SR and to some extent also for the IR patients. Relapses were significantly more common in the IR group in spite of a more intensive cytostatic regimen. The most decisive IR criteria were B-LPK and age at diagnosis. Prognosis was significantly worse for boys in all groups. After 3 years in CCR treatment was discontinued in 95 out of 246 children (38 %) of whom 19 later relapsed (20 %)

KEY WORDS: Childhood lymphoblastic leukemia, children, leukemia

Since 1967 the Swedish Child Leukemia Group (SCLG) has recommended a national uniform treatment of acute lymphoblastic leukemia (ALL) in children. The accumulated national experiences have increased the possibilities to evaluate the results of the treatment programs. In addition, it has been an advantage for parents and doctors in charge to know that children with ALL are treated according to the same principles in the whole country. This paper summarizes the results of treatment in Swedish children with ALL diagnosed between 1973 and 1978.

MATERIAL

All Swedish children (age <16 years at diagnosis) with diagnosed ALL from January 1973 to December 1978 are included in the material. The patients were evaluated according to their status in January 1980 with an observation time thus varying between 12 and 84 months.

During the actual period the estimated incidence was 3.4 children with ALL per 100 000 children per year.

The material comprises 367 children, 199 boys and 168 girls. Age and sex distributions are given in Fig. 1. Most cases occurred at 2½ years of age. There was also a small peak at 12½ years of age. In the ages 2–4 years and 9–13 years the incidence was higher for boys than for girls.

Three hundred and forty-five children were treated with the therapeutic programs of the SCLG listed in Table 1. These programs (III, IV_S, IV_I, V_S and V_I), in the years 1973 to 1978, imply a successively more intensified cytostatic therapy in addition to prophylactic cranial irradiation, Table 1. Therapy was discontinued after 3 years in continuous complete remission (CCR). For some reasons (see Discussion) 19 children were given other treatment than that recommended by SCLG, Table 1 (mixed group). Cranial irradiation was not given to these patients.

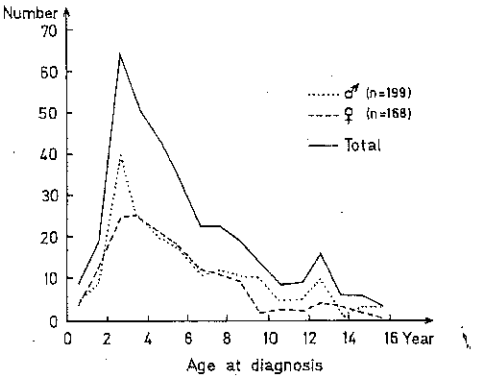

Fig. 1. Age and sex distribution at diagnosis.

Table 1. *The treatment programs of SCLG*

A = adriamycin, Asp = l-asparaginase, Cr = cranial irradiation, M = methotrexate intrathecally, Mtx = methotrexate orally, P = prednisolone, V = vincristine, 6-MP = mercaptopurine, Sdx = cyclophosphamide, Reind = reinduction, *n* = children with achieved remission

	Program	Induction	CNS	Maintenance
1973	III (n=161)	V×4, P	Cr, M×4	6-MP, Mtx (Sdx)
1976	IV_S (n=86)	V×6, P	Cr, M×6	6-MP, Mtx
	IV_I (n=35)	V×6, A×2, P, Ara-C	Cr, M×6	6-MP, Mtx, Reind
1978	V_S (n=37)	V×6, A×3, P	Cr, M×6	6-MP, Mtx
	V_I (n=16)	V×6, A×3, P, Asp	Cr, M×6	6-MP, Mtx, Reind
1973–78	Mixed (n=19)	Incomplete programs, No Cr.		

The children have been classified as suffering from leukemia with increased risk (IR) or standard risk (SR) according to criteria shown in Table 2. This classification started in 1976. The children with diagnosed ALL before this time have been classified retrospectively. Except for B-LPK, the same IR criteria have been used for the whole period. In 1978 the B-LPK level was reduced from $\geq 50\times10^9$/l to $\geq 20\times10^9$/l as an IR criterion, thus increasing the IR group with 5 children who would have been regarded as SR patients before that year. The IR group thus comprises 117 children (37%) and the SR group 250 children (63%). T- and B-celltyping of the leukemias did not start until 1978.

RESULTS

A survey of the patients is given in Table 3. Of 367 children with ALL 13 died within 6 weeks of diagnosis without achieving remission (6 IR and 7 SR children and 7 boys and 6 girls). Of the remaining 354 patients (i.e. 96% remission frequency) 17 died in CCR (11 due to infection, 5 due to unspecified encephalitis, 1 child in an accident).

During therapy 162 children relapsed, 69 of 111 children in the IR group (62%) and 93 of 243 children in the SR group (38%) Table 3. The relapses were significantly more frequent in the IR group than in the SR group ($p<0.01$). Most of the relapses were isolated, 102 in the bone marrow, 30 in the CNS and 7 in the testis. In 13 patients there were multifocal relapses with CNS involvement and in 10 patients there were multifocal relapses without CNS involvement. Three children with isolated CNS relapse had not received cranial irradiation. Thus, 40 of 335 children with prophylactic CNS treatment (cranial irradiation and intrathecal methotrexate) relapsed in CNS or CNS and bone marrow. Thirty-five of the 162 children who relapsed still live in a second or a third remission.

After 36 months in CCR (i.e. for the children with ALL diagnosed January 1973 to December 1976), treatment was discontinued

Table 2. *Criteria of increased risk in 117 children*

1 criterion in 73 children, 2 or more criteria in 44 children

	No. of children
Mediastinal mass	36
CNS-leukemia	17
B-LPK	81
Age <1 year >13 years	32
Total	166

Table 3. *The patient material 1973–1978*

IR = increased risk, SR = standard risk

	IR	ISR	Tot
Children with ALL	117	250	367
No remission	−6	−7	−13
Complete remission	111	243	354
Dead in CCR	−4	−13	−17
Relaps during therapy	−69	−93	−162
Relaps after therapy off	−4	−15	−19
Alive in CCR	34	122	156

ically, Mtx = methotrexate
ide, Reind = reinduction, *n*

nance

Mtx (Sdx)
Mtx
Mtx, Reind
Mtx
Mtx, Reind

ildren relapsed, 69 of
oup (62%) and 93 of
roup (38%) Table 3.
cantly more frequent
e SR group ($p<0.01$).
e isolated, 102 in the
CNS and 7 in the
ere were multifocal
rement and in 10 pa-
cal relapses without
children with isolat-
received cranial irra-
hildren with prophy-
anial irradiation and
relapsed in CNS or
Thirty-five of the 162
live in a second or a

R (i.e. for the chil-
ed January 1973 to
nt was discontinued

rial 1973–1978
lard risk

IR	ISR	Tot
117	250	367
−6	−7	−13
111	243	354
−4	−13	−17
−69	−93	−162
−4	−15	−19
34	122	156

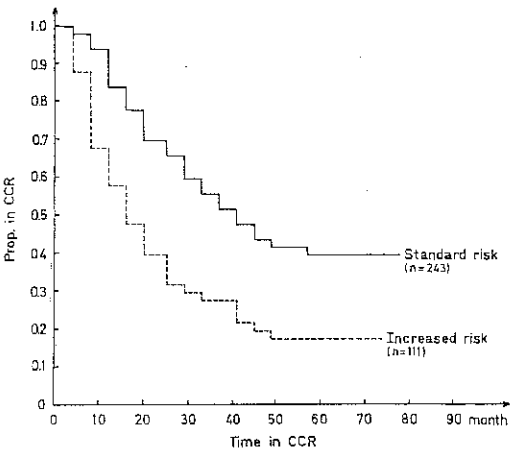

Fig. 2. Proportion in CCR for SR and IR patients, whole material.

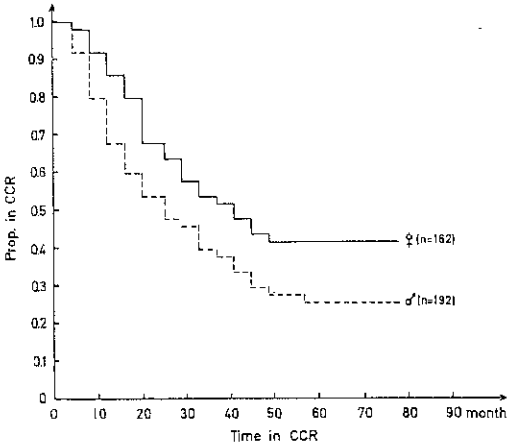

Fig. 4. Proportion in CCR for boys and girls, whole material.

in 95 out of 246 patients (38%), 47 boys and 48 girls, 81 in the SR group and 14 in the IR group. After discontinued therapy relapses occurred in 19 children (11 boys and 8 girls), 15 in the SR group and 4 in the IR group. Nine of these relapses occurred in the bone marrow, 1 in the CNS, 6 in the testis and 3 in more than one of these locations. Of the 19 relapses, 17 occurred during the first and 2 during the second year after cessation of therapy. No further relapses have as yet been noted during the third or fourth year after cessation of therapy.

The proportion of patients in CCR plotted against observation times are given in Figs. 2–8 according to a modified Kaplan-Meier method (1, 2). Fig. 2 shows the differences in diseasefree survival between the SR and the IR patients in the whole material. Fig. 3 gives the differences in survival in CCR for the various regimes used by SCLG. The survival in CCR was longer for girls than boys in all programs and Fig. 4 shows a significant difference in the whole material with a median survival of 39 months for the girls and 23 months for the

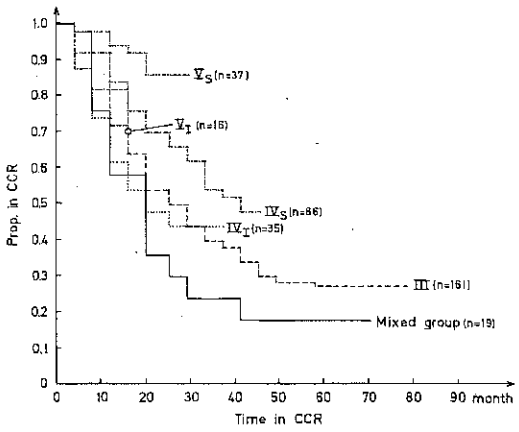

Fig. 3. Proportion in CCR with regard to the treatment programs used by SCLG, cf. Table 1.

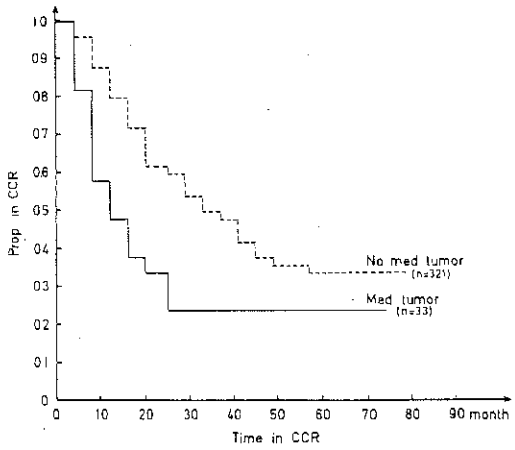

Fig. 5. Proportion in CCR for patients with and without mediastinal mass at diagnosis, whole material.

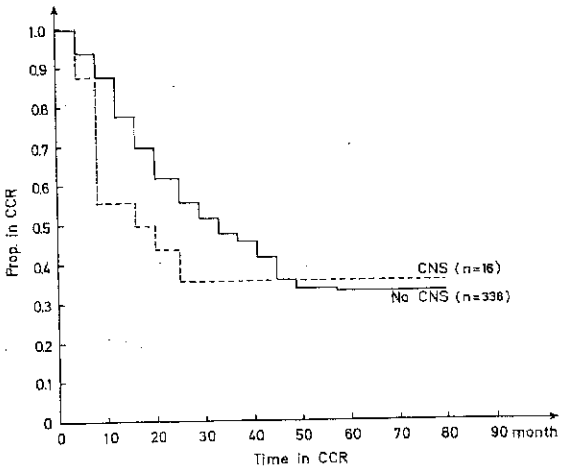

Fig. 6. Proportion in CCR for patients with and without CNS-involvement at diagnosis, whole material.

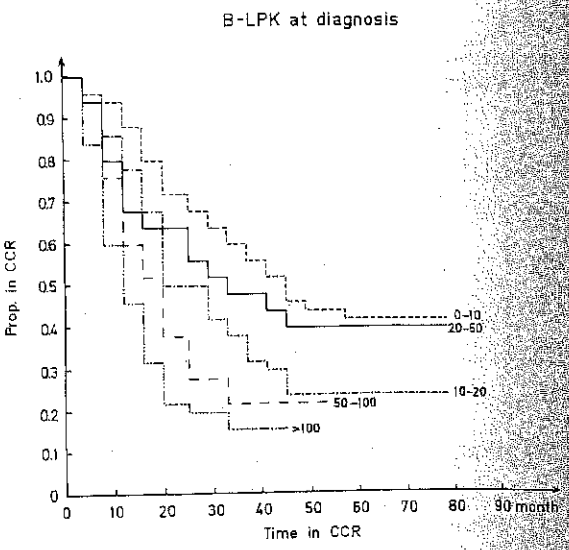

Fig. 8. Proportion in CCR with regard to B-LPK at diagnosis, whole material.

boys ($p<0.001$). Figs. 5–8 give the survival in CCR plotted against the IR criteria used.

DISCUSSION

Since 1967 the SCLG has given recommendations for national uniform treatment of ALL. The present material comprises all Swedish children with ALL diagnosed from January 1973 to December 1978, thus implying an incidence of 3.4 children with ALL per 100 000 children (age <16 years) per year.

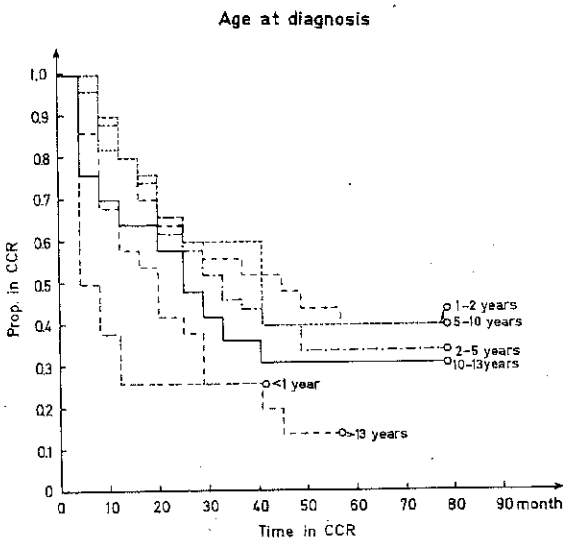

Fig. 7. Proportion in CCR with regard to age at diagnosis, whole material.

The treatment programs have been modified according to international experiences (3, 4) and the participation by the Swedish paediatric clinics has been high, 95% of the children attended the programs. The patients in the "mixed group" (Table 1) in our material were not selected with regard to clinical findings but belonged to regions where cranial irradiation was not accepted as CNS-prophylaxis, especially in the years 1973–1976. The present material thus enables an evaluation of the results of a national uniform treatment of ALL in an unselected material.

According to internationally accepted criteria (3, 4), Table 2, the patients have been classified into an SR group and an IR group. Fig. 2 explicitly shows the differences of diseasefree survival between the two groups in the whole material.

As shown in Fig. 3, intensification of cytostatic therapy will improve the results. Thus, programs IV and V have significantly longer survival times in CCR than program III. Program V_S has the best results with 84% of the patients in CCR, after an observation time of

t diagnosis

0–10
20–50

10–20
50–100

90

50 60 70 80 90 month
in CCR

regard to B-LPK at diag-

ith ALL per 100 000
per year.
s have been modified
l experiences (3, 4)
he Swedish paediat-
95% of the children
The patients in the
in our material were
clinical findings but
e cranial irradiation
S-prophylaxis, espe-
976. The present ma-
luation of the results
itment of ALL in an

nally accepted crite-
patients have been
ip and an IR group.
e differences of dis-
the two groups in

ensification of cyto-
e the results. Thus,
significantly longer
in program III. Pro-
ilts with 84% of the
observation time of

12–30 months (some patients started already during 1977). This is almost comparable with the best results reported by other groups (5).

Since 1976 the IR patients were also given a more intensive cytostatic induction therapy than the SR patients (programs IV and V). In spite of this, the survival in CCR was significantly shorter for the IR patients in both programs ($p<0.05$). The comparatively short survival time in CCR in the "mixed group" (Fig. 3) may be explained by the cautious induction regimen used in the years 1973–1976 when most of these patients were diagnosed. There were also proportionately more CNS-relapses in the "mixed group" but the materials are not statistically comparable in that respect.

The IR criteria are all associated with a decreased survival as shown by Figs. 5–8. In the IR group with mediastinal mass and CNS-involvement at diagnosis (Figs. 5 and 6) the relapses occur early and within 2 years of diagnosis. The relapses then cease in contrast with the other patients. With increased observation times the differences of survival in CCR, between patients with and without these criteria, thus diminish, and with regard to the CNS-involvement there are no differences after 4 years of observation. Similar findings have not been documented earlier. *They indicate the necessity of long follow-up periods before evaluating treatment results of ALL-regimens.*

The most decisive high risk criteria seemed to be age and B-LPK $>100\times10^9$/l at diagnosis (Figs. 7 and 8). The comparatively good survival for the patient group with B-LPK $20–50\times10^9$/l at diagnosis cannot merely be explained by the more intensive induction therapy these patients received after 1978 when they were classified as IR patients. Perhaps in the future, longer follow-up periods and B- and T-cell-typing of all children with ALL will bring further explanation to these findings.

The differences of survival in CCR between boys and girls are significant in the whole material and irrespective of age at diagnosis and treatment. The testicular relapses may to some part explain the differences. Male sex seems to be an IR criterion and boys perhaps need another sanctuary treatment than was used in our material (5).

Most of the relapses occurred in the bone marrow. The CNS relapses, on the whole, corresponded to 12 per cent of the patients receiving CNS prophylaxis. However, the frequency of CNS relapses has decreased in recent years as a result of an intensification of the CNS prophylaxis (programs IV and V) and in addition to some extent also to improved radiological technique. The relapses after discontinued therapy occurred within two years and mostly during the first year which is in agreement with international results (6).

Complications to therapy (especially infections and bleeding early in the course of the disease) have become more common throughout the years and were attributed mostly to the successively intensified cytostatic regimens in the induction period. The mortality in CCR could almost exclusively be ascribed to infections and has been reduced drastically in the years due to improved experiences in cytostatic and antibiotic therapy. Thus of 17 patients dead in CCR, 16 died before 1978.

ACKNOWLEDGEMENTS

We wish to express our most sincere thanks to Bertil W. Andersson for statistical and dataoperational work. The colleagues of 44 Swedish paediatric clinics and the members of the Swedish Child Leukemia Group are greatly acknowledged for provided information of the patients and valuable discussions. Financial support was obtained from the Swedish Cancer Society.

REFERENCES

1. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Statistic Assoc 1958; 53: 457–81.
2. Benedette J, Yven K. Life tables and survival functions. In: Braum MB, ed. Bio-Medical-Computer programs, P-series 1977. Berkeley, Los Angeles: University of California Press, 1977: 743–70.
3. Pinkel D. The ninth annual David Karnofsky lecture. Treatment of acute lymphocytic leukemia. Cancer 1979; 43: 1128–37.
4. Mauer AM. Therapy of acute lymphoblastic leukemia in childhood. Blood 1980; 56: 1–10.

5. Moe PJ, Seip M. High dose methotrexate in acute lymphocytic leukemia in childhood. Acta Paediatr Scand 1978; 67: 265–68.
6. George SL, Aur RJA, Mauer AM, Simone JV. A reappraisal of the results of stopping therapy in childhood leukemia. N Engl J Med 1979; 300: 269–73.

Submitted Nov. 3, 1980
Accepted Febr. 10, 1981
(G. G.) Department of Paediatrics
University Hospital
S-750 14 Uppsala
Sweden