PERGAMON

European Journal of Cancer 39 (2003) 952–960

European Journal of Cancer

www.ejconline.com

Population-based survival after childhood lymphoblastic leukaemia in time periods corresponding to specific clinical trials from 1979 to 1998—a report from the Childhood Cancer Registry of Piedmont (Italy)

G. Pastore[a,b], S. Viscomi[a], G.L. Gerov[c], B. Terracini[a], E. Madon[d], C. Magnani[a,e,*]

[a]*Childhood Cancer Registry of Piedmont, Cancer Epidemiology Unit of the Centre for Cancer Epidemiology and Prevention, CPO Piemonte, S.Giovanni Hospital, V. Santena 7, 10126 Turin, Italy*

[b]*Paediatric Department, S.Andrea Hospital, Vercelli, Italy*

[c]*Department of Social Medicine, Medical University, Plovdiv, Bulgaria*

[d]*Paediatric Oncology Department, Hospital for Sick Children 'Regina Margherita' and University of Torino, Turin, Italy*

[e]*Medical Statistics Unit, Department of Medical Sciences, Eastern Piedmont University at Novara, Italy*

Received 2 September 2002; received in revised form 2 December 2002; accepted 10 January 2003

Abstract

This study evaluated the outcome after childhood acute lymphoblastic leukaemia (ALL) in a population aged 0–14 years served by the Childhood Cancer Registry of Piedmont (CCRP) during the accrual periods to nationwide clinical studies run by the Italian Association for Paediatric Haematology and Oncology (AIEOP). In the time period considered (March 1979–December 1998) the CCRP recorded 498 incident cases of ALL. The living status on 31 December 2000 was known for 497 cases. Overall survival at 5 years was 74.1% standard error (S.E.) 2.0%). It increased from 58.6% (S.E. 4.9%) for cases diagnosed in March 1979–July 1982 to 87.3 (S.E. 3.6) in May 1995–December 1998. Results observed from data in our population-based study in Piedmont were similar to those presented in the nationwide clinical trials. Survival was better (statistically significant) for children aged 1–4 years, with a white blood cell (WBC) count lower than 10 000×10^3 cells/litre and for B-precursor ALL. Differences by immunophenotype were statistically significant only in the univariate analyses. Girls showed a non-statistically significant survival advantage over boys. Results of the present study show the impact on the population of recent clinical trials and emphasise the role of population-based cancer registries in evaluating childhood cancer care delivery in a given population.

Keywords: Acute lymphoblastic leukaemia; Prognosis; Survival; Epidemiology; Clinical studies; Population-based studies; Italy

1. Introduction

A remarkable improvement in survival for childhood acute lymphoblastic leukaemia (ALL) has been observed over the last three decades due to more effective treatments [1]. This has been achieved through a progressive improvement in the treatment protocols and their application in large sized, controlled clinical studies [2,3]. In industrialised countries, the results obtained in clinical trials undertaken in highly specialised clinical settings were soon reflected in population-based epidemiological (observational) studies, indicating that a large proportion of eligible cases of ALL were being recruited into the clinical studies [4–9].

Since the early 1970s, the therapeutic protocols for childhood leukaemias in Italy have been set up by the Italian Association for Paediatric Haematology and Oncology (Associazione Italiana di Ematologia e Oncologia Pediatrica (AIEOP)). AIEOP has had a major role in improving the already existing co-operation among Italian paediatric oncologists both in the clinical field and in the control of the quality of care [10]. AIEOP now includes 53 centres and is present in almost all Italian Regions. In 1989, a central database

* Corresponding author. Tel.: +39-011-633-6968; fax +39-011-633-6960.

E-mail address: corrado.magnani@cpo.it (C. Magnani).

0959-8049/03/$ - see front matter
doi:10.1016/S0959-8049(03)00064-9

was set up in order to describe the demographic and clinical features of children treated at those centres and to monitor the accrual of cases into multicentre protocols [11]. Since 1979, five consecutive protocols were launched by the AIEOP, whose design and results have been reported elsewhere in Refs. [10,12]. A short description of the protocols is presented in Table 1.

The present study intended to verify the impact of clinical trials on the general population, i.e the extent to which changes in survival rates estimated by a population-based cancer registry reflected contemporary results in clinical trials [7]. Additionally, we aimed to evaluate survival (overall and by time period) in subgroups defined by biological variables, in order to compare population-based results with the results reported by clinical trials.

2. Patients and methods

The Childhood Cancer Registry of Piedmont (CCRP) records incident cases of neoplasm in children (aged 0–14 years) resident in Piedmont (N.W. Italy). It started its activities in 1967 and the collection of cases is now updated to 31 December 1998. Cases are actively collected by trained personnel at 2–3 yearly intervals from hospital records and other relevant files. The registration is extended to all paediatric wards of the hospitals in the region and to other wards, both in Piedmont and elsewhere, where a child living in Piedmont and affected by a malignancy may be referred for diagnosis or treatment. Active registration is supplemented by a search of relevant cases in the files of pathology departments, of hospital admissions, of reimbursement for cancer treatment in other countries, and of cancer deaths, as well as in the AIEOP database [11]. Diagnoses are coded using the International Classification of Diseases for Oncology (ICD-O-1) classification and further grouped according to the International Classification for Childhood Cancer (ICCC) criteria [13].

During 1967–1998, the CCRP recorded 3072 cases of childhood malignancy, 1040 of which were leukaemias. The overall proportion of cases with a microscopic diagnosis was 96.3% among the leukaemia cases and 87.4% among cases of solid tumours. Cases are actively followed-up at regular intervals to ascertain their vital status and cause of death: for each child, the current living status was checked at the municipality where he/she was last known to live [14]. The most recent follow-up date was 31 December 2000. The size of the childhood population in Piedmont decreased during the time period considered in this report from approximately 800 000 in 1975–1979 to approximately 500 000 in 1995–1998, due to a reduction in the birth rates.

The present study included cases of ALL (ICCC category = 01A), incident in the time period of March 1979–December 1998. In the total of 498 cases, all, but one, were microscopically diagnosed and no cases were included on the basis of the death certificate only. In the same time period, the CCRP also recorded 106 incident cases of Acute non-lymphoblastic leukaemias (AnLL, ICCC category = 01B), 14 cases of chronic myeloid leukaemias (CML, ICCC category = 01C), 2 cases of other specified leukaemias (ICCC category = 01D) and 15 cases of unspecified leukaemias (ICCC category = 01E). These categories are not considered further in the present study.

Table 1
List of the AIEOP protocols for childhood ALL and correspondence with time periods in this study

Period of recruitment	AIEOP name and reference	Eligibility	Enrolled	Eligible and participated		Correspondence to time periods in this study
01.02.1976–28.02.1979	Study 76 [10]	Non-B ALL Age 1–14 years	428	428		Not included
01.03.1979–31.07.1982	Study 79 [10]	Non-B ALL Age 1–14 years	815	797	Enrolment for high-risk cases protracted to 03.1983	01.03.1979–31.07.1982
01.08.1982–28.02.1987	Study 82 [12]	Non-B ALL Age 1–14 years	977	902	The protocol for high-risk cases started in 1983 and was changed in 1985	01.08.1982–28.02.1987
01.03.1987–30.04.1991	Study 87 [12]	Non-B ALL Age 1–14 years	694	632	The two studies 87 and 88 were reported as 'largely similar' by Conter and colleagues [12]	01.03.1987–28.02.1991
01.02.1988–31.03.1991	Study 88 [12]	Non-B ALL Age 0–14 years	438	396		01.03.1987–28.02.1991
01.03.1991–30.04.1995	Study 91 [12]	Non-B ALL Age 0–14 years	1267	1194		01.03.1991–30.04.1995
01.05.1995–31.12.1999	Study 95	Non-B ALL Age 0–14 years			Results not yet published	01.05.1995–31.12.1998

AIEOP, Italian Association for Paediatric Haematology and Oncology; ALL, Acute Lymphoblastic Leukaemia.

The time period of this study was divided into five intervals, corresponding to the accrual in the different AIEOP protocols (Table 1). Since the individual information registered at the CCRP does not include whether or not the case had entered a trial, the date of diagnosis was used as a proxy. We estimated the survival rates of the children according to their period of diagnosis and some clinical prognostic variables: age, gender, white blood cell (WBC) count at diagnosis (missing for 5 cases, 1.0%) and immunophenotype (missing for 38 cases, 7.6%).

The cumulative survival probability was estimated using the product limit method [15]. The log rank test and the corresponding test for trend were used for estimating the statistical significance of differences in the survival probability among the subgroups [16]. Multivariate analyses were carried out using a Cox regression model [17] in order to estimate the Hazard Ratio (i.e. the ratio between the risk of death for individuals with given values of covariates relative to the risk for the individuals with covariates at the baseline) according to the time period and other prognostic variables. The Hazard Ratio can be interpreted in the same way as a Relative Risk. Plots of the cumulative hazard function $\{\log [-\log S(t)]\}$ were examined to detect deviations from the proportionality assumption of the Cox model [18].

3. Results

The data-set is described in Table 2. The proportion of ALL with unspecified immunophenotype gradually reduced from 20% in 1979–1982 to 1% since 1991. The trend observed in the distribution by age is dependent on changes in the size and structure of the childhood population and is not due to a reduction in the incidence rates. The other variables did not show any trends according to the time period of diagnosis. Only one case was lost to follow-up.

Survival changed substantially over the time period of diagnosis (Fig. 1). Survival at 5 years changed from 58.6% (S.E. 4.9) for cases diagnosed at the time of the protocol 'Study 79' (March 1979–July 1982) to 87.3% (S.E. 3.6) for those diagnosed after protocol 'Study 95' was introduced (May 1995 to the end of 1998). This trend was statistically significant (Table 3).

Table 3 provides the cumulative survival probability at 3, 5 and 10 years since diagnosis, estimated in the univariate analyses, both overall and stratified according to gender, age, immunophenotype, WBC ($\times 10^6$ cell/l) count and time period. The table also presents the Log-rank test P value (overall and, whenever appropriate, for the trend). Survival by age class was lowest for children diagnosed below 1 year of age and highest in those aged 1–4 years ($P = 0.017$). Pui and colleagues suggested to divide the age periods into wider intervals: less than 1 year, 1–9 and 10–14 years [1]: survival for children aged 1–9 years in our data-set was 83.3% at 3 years, 75.9% at 5 years and 72.8% at 10 years since diagnosis. Analyses were also carried out for age classes 0, 1–6 and 7–14 years, with very similar results. Girls showed a modest non-statistically significant advantage compared with boys. Survival by gender was further explored at increasing time intervals since diagnosis: no difference was observed at 6 months after diagnosis: (96% with a Confidence Interval (95% C.I.) 93–98% in both sexes); a small difference appeared after approximately 1–2 years and this became statistically significant after 10 years (males 67%, C.I. 61–73%; females 75%, 95% C.I. 69–80%) (Table 3). There was a highly significant trend towards a lower survival rate for children with increasingly high WBC counts (LR trend: $P < 0.001$). As for immunophenotypes, given the size of the groups, the only meaningful comparison was between children with T leukaemias and with B precursor leukaemias: the latter fared much better than the former ($P < 0.001$).

Less then 5% of children with ALL were treated in non-specialised hospital departments (11% in time period of 1975–1979; 6% in 1980–1984; 2% in 1985–1989 and 0% after 1990). The limited numbers precluded an analysis of the prognostic value of this factor.

Table 4 presents 5-year-cumulative survival by time period, stratified according to the prognostic factors. With allowance for the small numbers involved, a statistically significant trend in survival associated with the time period of diagnosis is evident in most strata. Exceptions were the following strata: age at diagnosis 10–14 years, WBC between 10 000 and 49 999, T cell, B cell (very few cases) and unspecified immunophenotype. Children aged 10–14 years already showed a good survival in the first time period with little change subsequently. Survival by WBC categories showed a significant trend in classes 'lower than or equal to 9999' and 'higher than or equal to 50 000'; figures

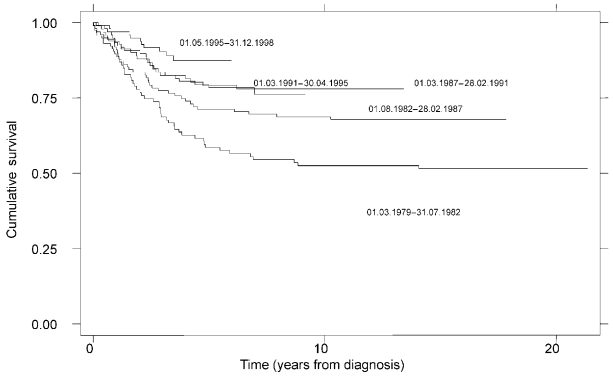

Fig. 1. Survival curves for childhood acute lymphoblastic leukaemia (ALL) in 1979–1998 in Piedmont by time period of diagnosis (see text).

Table 2
Frequency distribution (absolute and percent) of ALL cases diagnosed in 1979–1998 in Piedmont, according to gender, immunophenotype, WBC count, by age at diagnosis and period of diagnosis

		Time period of diagnosis					
		01.03.1979–31.12.1998 *N* (%)	01.03.1979–31.07.1982 *N* (%)	01.08.1982–28.02.1987 *N* (%)	01.03.1987–28.02.1991 *N* (%)	01.03.1991–30.04.1995 *N* (%)	01.05.1995–31.12.1998 *N* (%)
Total		498 (100)	99 (19.9)	115 (23.1)	91 (18.3)	97 (19.5)	96 (19.3)
Gender	Males	267 (53.6)	54 (54.5)	57 (49.6)	47 (51.6)	57 (58.8)	52 (54.2)
	Females	231 (46.4)	45 (45.5)	58 (50.4)	44 (48.4)	40 (41.2)	44 (45.8)
Immunophenotype	Not specified	35 (7.0)	20 (20.2)	8 (7.0)	5 (5.5)	1 (1.0)	1 (1.0)
	T	54 (10.8)	7 (7.1)	16 (13.9)	8 (8.8)	8 (8.2)	15 (15.6)
	B	12 (2.4)	0 (0.0)	0 (0.0)	1 (1.1)	6 (6.2)	5 (5.2)
	B precursor	397 (79.7)	72 (72.7)	91 (79.1)	77 (84.6)	82 (84.5)	75 (78.1)
WBC count	Missing	5 (1.0)	2 (2.0)	2 (1.7)	1 (1.1)	0 (0)	0 (0)
	$\leqslant 9999\times10^6$ cells/l	235 (47.2)	44 (44.4)	59 (51.3)	50 (54.9)	41 (42.3)	41 (42.7)
	10 000–49 999$\times10^6$ cells/l	167 (33.5)	43 (43.4)	28 (24.3)	24 (26.4)	37 (38.1)	35 (36.5)
	$\geqslant 50\ 000\times10^6$ cells/l	91 (18.3)	10 (10.1)	26 (22.6)	16 (17.6)	19 (19.6)	20 (20.8)
Age	Less than 1 year	13 (2.6)	3 (3.0)	3 (2.6)	3 (3.3)	2 (2.1)	2 (2.1)
	1–4 years	243 (48.8)	39 (39.4)	50 (43.5)	43 (47.3)	56 (57.7)	55 (57.3)
	5–9 years	156 (31.3)	36 (36.4)	37 (32.2)	30 (33.0)	25 (25.8)	28 (29.2)
	10–14 years	86 (17.3)	21 (21.2)	25 (21.7)	15 (16.5)	14 (14.4)	11 (11.5)

Table 3
Survival of cases of ALL diagnosed in 1979–1998 in Piedmont[a]

		No. observed	3 years CS (S.E.)	5 years CS (S.E.)	10 years CS (S.E.)	Log rank (*P* value)	Log-rank test for trend (*P* value)
Total		498	80.2 (1.8)	74.1 (2.0)	70.9 (2.1)		
Gender	Male	267	78.6 (2.5)	71.7 (2.8)	67.3 (3.0)	0.131	
	Female	231	82.0 (2.6)	77.0 (2.8)	75.0 (3.0)		
Age at diagnosis	Less than 1 year	13	53.8 (13.8)	53.8 (13.8)	53.8 (13.8)	0.017	
	1–4 years	243	87.1 (2.2)	79.1 (2.7)	75.8 (3.0)		
	5–9 years	156	77.3 (3.4)	70.9 (3.7)	68.2 (3.9)		
	10–14 years	86	69.7 (5.0)	68.5 (5.0)	64.2 (5.3)		
WBC count at diagnosis	Missing value	5	60.0 (21.9)	40.0 (21.9)	40.0 (21.9)	<0.001	<0.001
	$\leqslant 9999\times10^6$ cells/l	235	85.4 (2.3)	79.8 (2.7)	76.7 (2.9)		
	10 000–49 999×10^6 cells/l	167	82.6 (2.9)	76.0 (3.4)	70.5 (3.8)		
	$\geqslant = 50\ 000\times10^6$ cells/l	91	63.2 (5.1)	57.7 (5.4)	57.7 (5.4)		
Immunophenotype	Not specified	35	62.9 (8.2)	57.1 (8.4)	54.1 (8.4)	<0.001	
	T	54	61.9 (6.8)	57.3 (7.0)	57.3 (7.0)		
	B	12	83.3 (10.8)	83.3 (10.8)	83.3 (10.8)		
	B precursor	397	84.0 (1.8)	77.6 (2.1)	73.9 (2.3)		
Time period of diagnosis	01.03.1979–31.07.1982	99	68.7 (4.7)	58.6 (4.9)	52.5 (5.1)	<0.001	<0.001
	01.08.1982–28.02.1987	115	77.4 (3.9)	71.3 (4.2)	68.7 (4.3)		
	01.03.1987–28.02.1991	91	82.4 (4.0)	79.1 (4.3)	78.0 (4.3)		
	01.03.1991–30.04.1995	97	83.5 (3.8)	78.3 (4.2)	–		
	01.05.1995–31.12.1998	96	90.3 (3.1)	87.3 (3.6)	–		

WBC, white blood cell.
[a] Cumulative survival percent (CS) and corresponding standard error (S.E.) at 3, 5 and 10 years after diagnosis, stratified according to prognostic factors. The table shows the *P* value computed according to the Log-rank test for the difference in survival among the different groups and for the linear trend.

were suggestive for a trend also in the category '10 000–49 999', but statistical significance was not achieved.

Results of multivariate analyses with the Cox model are presented in Table 5. The final model included time period of diagnosis, age at diagnosis and WBC count: it showed a better survival for children diagnosed in the more recent time periods, while it showed a poorer outcome for children diagnosed before the age of 1 year or with a higher WBC count. Neither gender or immunophenotype contributed significantly to the model fit and were not confounders. They were therefore not retained.

4. Discussion

The novelty of the present study lies in the evaluation of the impact of clinical trials as observed from a population-based perspective, with consideration of some prognostic factors. The significant rise in survival for the children affected by ALL can be attributed to the better diagnostic and therapeutic approaches that have been implemented in the last 30 years. Such improvements led not only to more effective treatment options, but also to an improved risk stratification and thus more precise treatment plans [1,19]. Our study showed that the progressive improvement of the survival rate of children with ALL observed in clinical studies in Italy [10,12] can be detected through a population-based registry. Corresponding results have been presented from other countries [8,21]. The proportion of incident ALL cases that were included in the clinical studies increased over the time period examined according to our estimates based on the expected number of cases in Italy [22] and on the number of cases recruited according to the reports of the clinical studies [10,12], the estimated nationwide coverage was 57% for Study 79 (1 March 1979–31 July 1982), 50% for Study 82 (1 August 1982–28 February 1987), 66% for Studies 87 and 88 (1 March 1987–28 February 1991) and 83% for Study 91 (1 March 1991–30 April 1995). Results for Study 95 (since May 1995) have not yet been published. Coverage of cases resident in Piedmont was not lower, although exact figures were not reported.

Results of the present study are based on high quality data throughout the entire time period, as measured by the proportion of cases with microscopic diagnosis and

Table 4
Five-year cumulative survival in percent and corresponding standard errors (S.E., in parentheses), stratified by prognostic variable and time period of diagnosis[a]

		01.03.1979–31.07.1982	01.08.1982–28.02.1987	01.03.1987–28.02.1991	01.03.1991–30.04.1995	01.05.1995–31.12.1998	*P* value
Age at diagnosis	Less than 1 year	33.3 (27.2)	0.0	66.7 (27.2)	100.0 (–)	100.0 (–)	0.047
	1–4 years	56.4 (7.9)	78.0 (5.9)	81.4 (5.9)	87.5 (4.4)	89.3 (4.6)	<0.001
	5–9 years	52.8 (8.3)	75.7 (7.0)	73.3 (8.1)	72.0 (9.0)	88.2 (6.5)	0.011
	10–14 years	76.2 (9.3)	60.0 (9.8)	86.7 (8.8)	50.0 (13.4)	72.7 (13.4)	0.939
Gender	Male	61.1 (6.6)	68.4 (6.2)	76.6 (6.2)	71.9 (5.9)	83.9 (5.2)	0.011
	Female	55.6 (7.4)	74.1 (5.7)	81.8 (5.8)	87.5 (5.2)	91.1 (5.2)	<0.001
WBC at diagnosis	$\leqslant 9999\times10^6$ cells/l	63.6 (7.2)	72.9 (5.6)	86.0 (4.9)	87.8 (5.1)	95.1 (3.4)	<0.001
	10 000–49 999×10^6 cells/l	67.4 (7.1)	82.1 (7.2)	75.0 (8.8)	75.7 (7.0)	83.6 (6.8)	0.119
	$\geqslant 50\ 000\times10^6$ cells/l	10.0 (9.5)	57.7 (9.7)	62.5 (12.1)	63.2 (11.1)	77.9 (10.0)	0.005
	Missing	0.0 (–)	50.0 (35.4)	100.0 (–)	–	–	0.263
Immunophenotype	T	42.9 (18.7)	56.2 (12.4)	50.0 (17.7)	62.5 (17.1)	67.5 (14.0)	0.260
	B	–	–	100.0 (–)	66.7 (19.2)	100.0 (–)	0.436
	B precursor	58.3 (5.8)	75.8 (4.5)	84.4 (4.1)	81.7 (4.3)	89.6 (38.1)	<0.001
	Not specified	65.0 (10.7)	50.0 (17.7)	40.0 (21.9)	0.0 (–)	100.0 (–)	0.372

WBC, white blood cell.
[a] The last column shows the *P* value corresponding to the χ^2 test for a linear trend in survival over the time period.

Table 5
Multivariate survival analyses of ALL cases diagnosed in 1979–1998 in Piedmont[a]

	HR	95% C.I.
Time period of diagnosis		
01.03.1979–31.07.1982	1[b]	–
01.08.1982–28.02.1987	0.55	0.35–0.86
01.03.1987–28.02.1991	0.38	0.22–0.65
01.03.1991–30.04.1995	0.42	0.25–0.71
01.05.1995–31.12.1998	0.24	0.12–0.48
Age at diagnosis		
Less than 1 year	2.07	0.88–4.87
1–4 years	1[b]	–
5–9 years	1.34	0.90–1.99
10–14 years	1.51	0.96–2.37
WBC count at diagnosis ($\times 10^6$ cells/l)		
$\leqslant$9999	1[b]	–
10 000–49 999	1.25	0.83–1.86
$\geqslant$50 000	2.63	1.70–4.06
Missing	2.14	0.66–6.94

The model included time period of diagnosis, age at diagnosis and white blood cell (WBC) count.

[a] The Hazard Ratio (HR) and the corresponding 95% confidence interval (95% C.I.) were computed according to the Cox model.

[b] Reference category.

known immunophenotype and the completeness of follow-up.

The information recorded at CCRP did not allow us to estimate survival rates according to the actual treatment given to each individual. Admittedly, using time periods defined as the date of accrual of the AIEOP trials as a proxy may have resulted in some imprecision. Indeed, when comparing the outcome at 5 years for children living in Piedmont and all Italian children entering each nationwide AIEOP trial [12], no differences were observed (Table 6).

Our study also provided population-based information on survival and survival trends according to some well-known prognostic factors such as age, gender, immunophenotype and WBC at diagnosis [1]. These biological and clinical data are easy to collect and have powerful prognostic relevance. In this respect, our expectation was to observe the same differences and trends as reported in the clinical trials. Different findings would point either to limitations in the application of data from clinical studies to the general population or to the effects of selection at entry.

Over the whole time period, the results according to age at diagnosis did not differ from those expected [20]: The group aged 1–4 years at diagnosis experienced the best survival rates; survival was poorest for infants (risk of death twice that of children aged 1–4 years); children aged 5–9 years had an approximately 30% and children aged 10–14 years an approximately 50% increase in the risk of death (both were not statistically significant) compared with children aged 1–4 years. Concerning changes over the time period of diagnosis by age class, we observed a positive trend for all classes except for children aged 10–14 years. The interpretation of this result is not obvious: we noted that survival for children aged 10–14 years in the first time period examined was higher then that observed in other population-based studies (e.g. 76.2% at 5 years in 1979–1982, compared with 54% in the UK in 1980–1984 [8]). In the following time periods, the survival rate remained high, but fluctuated, as can be expected due to the small numbers involved. Our results did not differ from those observed in the AIEOP clinical trials in Italy and do not suggest a limited application of protocols in this age class: according to Conter an colleagues [12], event-free survival in the age class of 10+ years was 46.3% in 'Study 82', 48.9% in 'Study 87', 61.1% in 'Study 88' and 52.5% in 'Study 91'. Although it is evident that results in older children are more limited than in younger ones, the interpretation of the limits of the therapies exceeds the scope of the present work.

A better prognosis for girls than for boys has been reported in the literature [21]. However, recent

Table 6
Five-year survival percent and corresponding standard errors (S.E.) for the time periods considered in the CCRP study and for the corresponding nationwide AIEOP clinical trials[a]

	01.03.1979–31.07.1982	01.08.1982–28.02.1987	01.03.1987–28.02.1991	01.03.1991–30.04.1995	01.05.1995–31.12.1998
Our results	59.4 (S.E. 5.0)	73.2 (S.E. 4.2)	78.9 (S.E. 4.3)	79.1 (S.E. 4.3)	86.7 (S.E. 3.8)
AIEOP [10]	63 (S.E. not available)[b]				
AIEOP [12]		70.4 (S.E. 1.5)	78.7 (S.E. 1.7)[c] 78.1 (S.E. 2.1)[d]	79.4 (S.E. 1.2)	Results not yet available

See Table 1 for details on clinical trials.

[a] In order to increase comparability, we applied in the present table the same eligibility criteria adopted in the AIEOP clinical trials (i.e. non-B ALL and, limited to the first two periods, age 1 year or older).

[b] Survival results for trials AIEOP 76 (accrual period 2/76–2/79), AIEOP 79 (accrual period 3/79–7/82) and AIEOP 82 (accrual period limited to 7/82–7/86) were presented together.

[c] Trial AIEOP 87.

[d] Trial AIEOP 88.

epidemiological studies show that gender accounts for only a minor difference in cumulative survival (5% at 5 years in the EUROCARE study [23]), which is statistically significant in very large databases only. The present study is not at variance with this reported data: prognosis was better for girls, both in the overall analyses and in the analyses by time period, but the difference with boys did not reach statistical significance. Both sexes benefited from changes implemented in clinical trials. When survival was analysed at increasing time intervals, the difference between the genders was not apparent shortly after diagnosis, but become significant when long-term follow-up was considered (this observation reflected only the experience of the first trials, due to the longer period of follow-up). In this respect, our results parallel those presented by Stiller and Eatock [21].

Results by immunophenotype showed a statistically significant trend related to the time of diagnosis for B-precursor ALL, while they were not consistent for T-ALL and B-ALL. Immunophenotype was no longer significant in the multivariate analyses. The time trend by immunophenotype must be evaluated with consideration of the effect of the time period due to improvements in diagnostic techniques. Almost all of the unspecified leukaemia cases were diagnosed in the first time periods (Table 2) and showed a poor survival, both overall (Table 3), and in analyses stratified by time period (Table 4). However, in the first two time periods, there were no cases diagnosed as B-ALL while the 'not specified' leukaemia cases accounted for a substantial proportion (20 cases—20.2% in the period 1979–1982) (Table 2). It is likely that in the first time periods, B-ALL were misdiagnosed as either in the B precursor or in the unspecified ALL category. This is therefore the most likely explanation for the good survival of B-ALL in the overall analyses. However, we must note that B-ALL were not included in the AIEOP clinical trials [10,12]. Stiller and Eatock observed a statistically significant difference by immunophenotype limited to the 2-year time period after diagnosis [21].

Prognosis was better for children with WBC $\leqslant 9999\times10^3$ cells/l and this worsened with increasing WBC count. A positive trend in prognosis over the time period of diagnosis was observed for all WBC categories, but WBC at the time of diagnosis is still an important predictor of outcome, even for children diagnosed in the most recent time period. A positive trend over the time periods of diagnosis was observed for all WBC categories (Tables 4 and 5). As for the other prognostic factors considered, these results are in agreement with the AIEOP clinical trials [10,12] and most studies, such as the recent report by Donadieu and colleagues [20], although the different strategies adopted for defining categories in the analyses precluded an exact comparison.

In conclusion, this report documents the positive results observed in the care of ALL in childhood in Piedmont and the agreement of population-based results with those expected from clinical trials. We expect that a corresponding trend in survival applies to the entire country, given the increasing proportion of children enrolled in clinical trials. An indirect suggestion in favour of this hypothesis comes from the reduction of mortality rates for childhood leukaemias [24]. This paper shows the feasibility and interest in monitoring the population impact of clinical studies, both overall, and with consideration of biological prognostic factors. Our results also stress the importance and usefulness of close co-operation between clinicians and epidemiologists.

Acknowledgements

Dr. Gerov's participation was granted by an International Union Against Cancer (UICC) fellowship. A grateful thank-you to Prof. Luca Cordero di Montezemolo for his comments and to Mrs. Marinella Nonnato for the careful management of the CCRP data and the follow-up. The activity of the Childhood Cancer Registry is supported by the Piemonte Region and by the Italian Association for Research on Cancer (AIRC).

References

1. Pui CH, Evans EV. Acute lymphoblastic leukemia. *N Engl J Med* 1998, **339**, 605–614.
2. Chessells JM, Richards SM, Bailey CC, Lilleyman JS, Eden OB. Gender and treatment outcome in childhood lymphoblastic leukaemia: report from the MRC UKALL trials. *Br J Haematol* 1995, **89**, 364–372.
3. Richards S, Burrett J, Hann I, Chessells J, Hill F, Bailey C. Improved survival with early intensification: combined results from the Medical Research Council childhood ALL randomised trials, UKALL X and UKALL XI. Medical Research Council Working Party on Childhood Leukaemia. *Leukemia* 1998, **12**, 1031–1036.
4. Stiller CA, Draper GJ. Treatment centre size, entry to trials, and survival in acute lymphoblastic leukaemia. *Arch Dis Child* 1989, **64**, 657–661.
5. Stiller CA, Bunch KJ. Trends in survival for childhood cancer in Britain diagnosed 1971–85. *Br J Cancer* 1990, **62**, 806–815.
6. Stiller CA. Population based survival rates for childhood cancer in Britain, 1980–91. *Br Med J* 1994, **309**, 1612–1616.
7. Pastore G, Mosso ML, Carnevale F, *et al*. Survival trends of childhood cancer diagnosed during 1970–1994 in Piedmont, Italy: a report from the Childhood Cancer Registry. *Med Pediatr Oncol* 2001, **36**, 481–488.
8. Brenner H, Kaatsch P, Burkhardt-Hammer T, Harms DO, Schrappe M, Michaelis J. Long-term survival of children with leukemia achieved by the end of the second millennium. *Cancer* 2001, **92**, 1977–1983.
9. Ries LA, Eisner MP, Kosary CL, *et al*. Childhood cancer by the ICCC. In *SEER Cancer Statistics Review*, *1973–1998*. Bethesda, MD, National Cancer Institute, 2001, 1.
10. Paolucci G, Masera G, Vecchi V, Marsoni S, Pession A, Zurlo MG. Treating childhood acute lymphoblastic leukaemia (ALL): summary of ten years' experience in Italy. ALL Steering

Committee of the Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP). *Med Pediatr Oncol* 1989, **17**, 83–91.
11. Pession A, Rondelli R, Haupt R, *et al*. Sistema di rilevazione dei casi di tumore maligno in età pediatrica in Italia su base ospedaliera. *Riv Ital Pediatr* 2000, **26**, 333–341.
12. Conter V, Aricò M, Valsecchi MG, *et al*. Long-term results of the Italian Association of Pediatric Hematology and Oncology (AIEOP) acute lymphoblastic leukemia studies, 1982–1995. *Leukemia* 2000, **14**, 2196–2204.
13. Kramarova E, Stiller C. The international classification of childhood cancer. *Int J Cancer* 1996, **68**, 756–765.
14. Magnani C, Mosso ML, Colombo R, *et al*. The Childhood Cancer Registry of Piedmont. In Parkin DM, Kramarova E, Draper G, *et al*, eds. *International Incidence of Childhood Cancer,* vol II. Lyon, International Agency for Research on Cancer, 1998, 311–313.
15. Kaplan EL, Meier P. Non parametric estimation from incomplete observations. *J A Stat Assoc* 1958, **53**, 457–481.
16. Peto R, Pike MC, Armitage P, *et al*. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. analysis and examples. *Br J Cancer* 1977, **35**, 1–39.
17. Cox D. Regression models and life-tables. *J R Soc Stat* 1972, **34**, 187–220.
18. Marubini E, Valsecchi MG. *Analysing Survival Data from Clinical Trials and Observational Studies*. New York, Wiley, 1995.
19. Smith M, Arthur D, Camitta B, *et al*. Uniform approach to risk classification and treatment assignment for children with acute lymphoblastic leukemia. *J Clin Oncol* 1996, **14**, 18–24.
20. Donadieu J, Auclerc MF, Baruchel A, *et al*. Prognostic study of continuous variables (white blood cell count, peripheral blast cell count, haemoglobin level, platelet count and age) in childhood acute lymphoblastic leukaemia. Analysis of a population of 1545 children treated by the French Acute Lymphoblastic Leukaemia Group (FRALLE). *Br J Cancer* 2000, **83**, 1617–1622.
21. Stiller CA, Eatock EM. Patterns of care and survival for children with acute lymphoblastic leukaemia diagnosed between 1980 and 1994. *Arch Dis Child* 1999, **81**, 202–208.
22. Magnani C, Capocaccia R, Giordano L, *et al*. Stima del numero di casi incidenti di tumore maligno in età pediatrica in Italia, per regione. *La Rivista Italiana di Pediatria* 1992, **18**, 203–207.
23. Coebergh JW, Pastore G, Gatta G, Corazziari I, Kamps W. Variation in survival of European children with acute lymphoblastic leukaemia, diagnosed in 1978–1992: the EUROCARE study. *Eur J Cancer* 2001, **37**, 687–694.
24. Levi F, LaVecchia C, Negri E, Lucchini F. Childhood cancer mortality in Europe, 1955–95. *Eur J Cancer* 2001, **37**, 785–809.