PERGAMON

European Journal of Cancer 37 (2001) 695–702

European Journal of Cancer

www.ejconline.com

Survival from acute non-lymphocytic leukaemia (ANLL) and chronic myeloid leukaemia (CML) in European children since 1978: a population-based study

G. Gatta [a,*], R. Luksch [b], M.P. Coleman [c], I. Corazziari [d] and the EUROCARE Working Group

[a] *Istituto Nazionale per lo Studio e la Cura e dei Tumori, Divisione di Epidemiologia, Via Venezian,1, 20133 Milan, Italy*
[b] *Istituto Nazionale per lo Studio e la Cura e dei Tumori, Unità Operativa di Pediatria, Via Venezian,1, 20133 Milan, Italy*
[c] *London School of Hygiene and Tropical Medicine, London, UK*
[d] *Istituto Superiore di Sanità, Laboratorio di Epidemiologia e Biostatistica, Viale Regina Elena, 299, 00161 Rome, Italy*

Received 9 October 2000; accepted 29 December 2000

Abstract

We used data supplied by population-based cancer registries, collected and quality controlled using a common protocol, to analyse survival from acute non-lymphocytic leukaemia (ANLL) and chronic myeloid leukaemia (CML) among children in 17 European countries. Variations in survival in relation to age, country, histologic subtype and period of diagnosis (1978–1992) were examined. These are rare malignancies and survival can be studied reliably only by examination of data from a very large population (in this case EUROCARE). 5 years after diagnosis, overall survival was 44% (95% CI 33–55) for CML and 37% (95% CI 32–43) for ANLL. For both types of leukaemia, survival was slightly better for girls and worse in children under 5 years of age. Consistent with clinical literature, the ANLL subtypes with poorer prognosis were monocytic, megakaryocytic and erythroleukaemia. For ANLL, 5-year survival was better in Finland, the UK, The Netherlands and Germany ($\geqslant$40%); for CML, 5-year survival was highest in Italy, although the 95% CI were wide. The risk of death from ANLL and CML fell by 7% per year and 5% per year, respectively, after adjustment for age, gender and country. Since these rare childhood malignancies were virtually untreatable until 1970, these are very welcome trends.

Keywords: Childhood cancer; Population-based cancer registries; Survival; Survival trends; Gender contrast; Chronic myeloid leukaemia; Acute non-lymphocytic leukaemia; Europe

1. Introduction

Acute non-lymphocytic leukaemia (ANLL) in children is a rare disease; chronic myeloid leukaemia (CML) is rarer still. In Europe, ANLL incidence rates are between 9 and 4 per million children per year, while the incidence of CML is approximately 1 per million per year [1]. ANLL and CML accounts for 20–25% of all newly diagnosed leukaemias in children less than 15 years of age, with approximately 300–350 new cases per year in the European Union [2]. Survival for children with these kinds of leukaemia has improved over the last 20 years, however, prognosis remains fairly poor. Current chemotherapy regimens cure only 30–40% of children with ANLL, and are ineffective against CML without allogeneic bone marrow transplantation [3]. Studies report higher survival rates for children with leukaemia treated at paediatric cancer centres or as part of clinical trials [4], and to improve clinical results, it is advised that these children be treated as part of clinical trials, if possible at specialist treatment centres [5].

Population-based survival studies document the impact of efforts to cure these cancers, as they can reveal whether new treatment guidelines for childhood cancer are being implemented on a large scale. The

* Corresponding author. Tel.: +39-2-239-0460; fax: +39-02-239-0762.
E-mail address: gatta@anprisc.anapat.istitutotumori.mi.it (G. Gatta).

0959-8049/01/$ - see front matter
PII: S0959-8049(01)00045-4

EUROCARE data-base provides a unique opportunity to compare survival in different European populations for these rare leukaemia histotypes: the database contains data on approximately 45 000 childhood cancer cases diagnosed between 1978 and 1992 [6], and the uniform data collection policy, data checking and analytical procedures were agreed in advance between the 45 participating European cancer registries. EUROCARE I produced survival analyses for all types of leukaemia grouped together (ICD9 204–208) diagnosed in 12 countries during the period 1978–1985 [7]. As a result of the implementation of the International Classification of Childhood Cancer (ICCC) [8] in the EUROCARE II project, it is now possible to analyse the leukaemia group in greater detail. In addition, more countries and registries are participating in EUROCARE II [9] than in the first EUROCARE study.

The aim of this study was to describe survival for European children diagnosed with ANLL or CML, elucidating differences in relation to age, gender and country for the period 1985–1989. Changes in prognosis with time are also explored during the period 1978–1992. A survival analysis for acute lymphocytic leukaemia (ALL) is published separately [10].

2. Patients and methods

We considered all children diagnosed with ANLL (ICCC Ib) and CML (ICCC Ic) for whom complete follow-up data were available (minimum follow-up 5 years), recorded by population-based cancer registries in 17 European countries. These data represent the childhood leukaemias from a population base of about 134 million [11]. Both microscopically verified and non-verified cases were included, but cases known to registries by death certificate only (DCO) or discovered incidentally at autopsy were excluded. Descriptions of the cancer registries, their data gathering methods, and the standardised procedures for ensuring data comparability and quality were published in the first and second EUROCARE monographs and in the article by Magnani in this issue [6,7,9].

Table 1 shows the 915 ANLL and 148 CML children diagnosed during the study period (1985–1989) according to country. The registries of Finland, Denmark, Iceland, England and Wales, Scotland, The Netherlands, West Germany, Estonia, Slovakia and Slovenia cover the entire populations of those countries. Other countries are represented by one or more local or

Table 1
European cases of childhood ANLL and CML by country, diagnosed in 1985–1989, with indicators of data quality[a,b]

Registries from:	No. of cases		No. of boys		No. 0–4 years of age		% MV		No. lost to follow-up		Of all leukaemias	
	ANLL	CML	ANLL	CML	ANLL	CML	ANLL	CML	ANLL	CML	% Unspecified	% ANLL and CML
Northern Europe												
Denmark	31	6	12	3	20	4	100.0	100.0	0	0	0.5	17.5
Finland	29	2	11	1	17	2	100.0	100.0	0	0	0.9	14.2
Iceland	2	0	1	0	0	0	100.0	100.0	0	0	14.3	14.3
Sweden	10	1	4	1	6	0	100.0	100.0	0	0	–	19.6
UK												
England and Wales	303	46	153	29	142	22	99.3	100.0	0	0	3.7	19.1
Scotland	27	6	12	3	14	4	100.0	100.0	0	0	0.5	16.8
Western and Central Europe												
France	17	0	6	0	8	0	94.1	–	0	0	2.7	22.7
Germany (West)	283	55	157	32	136	23	100.0	100.0	4	2	1.1	17.0
Switzerland	1	1	1	1	0	1	100.0	100.0	0	0	–	18.2
The Netherlands	82	3	36	0	31	2	100.0	100.0	1	0	3.7	17.7
West Southern Europe												
Italy	47	8	23	4	20	2	83.0	75.0	0	1	3.0	20.5
Spain	19	3	13	3	5	1	100.0	100.0	0	0	4.7	5.0
Eastern Europe												
Estonia	6	2	3	0	4	1	100.0	100.0	1	0	13.5	15.4
Poland	8	0	2	0	5	0	100.0	–	0	0	–	17.4
Slovakia	38	12	18	8	11	9	100.0	100.0	0	0	1.3	21.3
Slovenia	12	3	6	2	4	0	100.0	100.0	0	0	1.5	22.1
Europe	915	148	458	87	423	71	99.0	98.7	6	3	1.5	18.2

MV, microscopically verified; ANLL, acute non-lymphocytic leukaemia; CML, chronic myeloid leukaemia.

[a] The national registries are in bold.

[b] Source of data: EUROCARE.

regional registries. The majority of cases were reported by the childhood cancer registries of England and Wales ($n = 303$, 33% and West Germany (n = 283, 31%). Table 1 also shows the number of boys (50% in ANLL and 59% in CML), children aged 0–4 years 46% in ANLL and 48% in CML), microscopically verified cases (approximately 99%, ranging from 75–100%), and number of cases lost to follow-up ($n = 6$ for ANLL and $n = 3$ for CML).

As an indicator of the quality of diagnosis in each country, Table 1 includes the proportions of all leukaemias in children that were either ANLL or CML (18%), and the proportion that were of an unspecified type (1.5%). The first of these proportions indicates the ability of treatment centres in the territory covered by the registry to distinguish between lymphoid and myeloid leukaemias, which in turn depends on the availability and use of specific markers.

Trends in survival over time were analysed only for countries whose registries provided data for the whole period 1978–1989 and had a minimum number of cases. For ANLL, eight countries had at least 30 cases (Denmark, The Netherlands, England and Wales, Finland, Germany, Italy, Scotland, Slovakia) with a total of 1811 patients. For CML, five countries had a minimum number of 15 cases (The Netherlands, England and Wales, Germany, Scotland, Slovakia) with a total of 278 cases. A further trend survival analysis was made using data for children diagnosed in 1978–1992, followed for a maximum of 3 years, from registries that provided data for the whole period [6], designed to investigate differences in survival in the most recent period. These results are reported in the Discussion.

For international survival comparisons, the European survival rates for the period of 1978–1989 were presented, in order to provide a more reliable comparison with the survival figures in other non-European areas.

Observed survival rates were calculated by the actuarial method [12]. Overall European survival was estimated as the weighted average of the survival of each country. Weights were proportional to the childhood population (0–14 years) in each country (Table 2 of Ref. [6]), assuming that the survival of patients from countries not entirely covered by the registration is representative of survival at the national level. Because survival is usually dependent on patients' age and the age distribution of children may differ between countries, to examine intercountry variation, direct age-standardised survival rates were calculated [13] from age-specific rates for three age classes: 0–4, 5–9 and 10–14 years. The age distribution of cases in the overall European sample was used as the standard. For Europe, the age-standardised survival rates were from the weighted European age-specific survival figures.

Survival was compared for three successive 4-year periods of diagnosis 1978–1981, 1982–1985, 1986–1989 using the Cox proportional hazard models [14] adjusted for age, gender and country.

3. Results

The weighted European survival rates up to 5 years after diagnosis for childhood ANLL and CML are shown in Fig. 1. Survival for CML was slightly better than for ANLL 5 years after diagnosis (44% versus 37%). For ANLL, survival declined markedly during the 3-years after diagnosis (from 57% at 1 year to 39% at 3 years), but there was little difference between 3- and 5-year survival (39 and 37%). By contrast, survival for

Table 2
Distribution of ICCC subcategories of ANLL and CML, in children < 15 years, both genders, with 5-year survival rates: EUROCARE, children diagnosed 1985–1989[a]

Diagnostic group	ICD-O code	Number and % of cases by gender			5-year survival (%) (95% CI)
		All No. (%)	Boys No.	Girls No.	
Ib: Acute non-lymphocytic					
	9840: Erythroleukaemia	19 (2.1)	12	7	26 (12–49)
	9841: Acute erythremia	2 (0.2)	1	1	0 (34–100)
	9861: Acute myeloid leukaemia	745 (81.4)	369	376	42 (38–46)
	9866: Acute promyelocytic	40 (4.4)	24	16	48 (33–63)
	9867: Acute myelomonocytic	1 (0.1)	1	0	0 (21–100)
	9891: Acute monocytic leukaemia	78 (8.5)	38	40	35 (25–46)
	9910: Acute megakaryoblastic	30 (3.3)	12	18	27 (14–44)
Ic: Chronic myeloid					
	9863: Chronic myeloid leukaemia	132 (89.2)	76	56	27 (20–37)
	9868: Chronic myelomonocytic leukaemia	16 (10.8)	11	5	31 (14–50)

ICCC, International Classification of Childhood Cancer; ANLL, acute non-lymphocytic leukaemia; CML, chronic myeloid leukaemia.
[a] Source of data: EUROCARE.

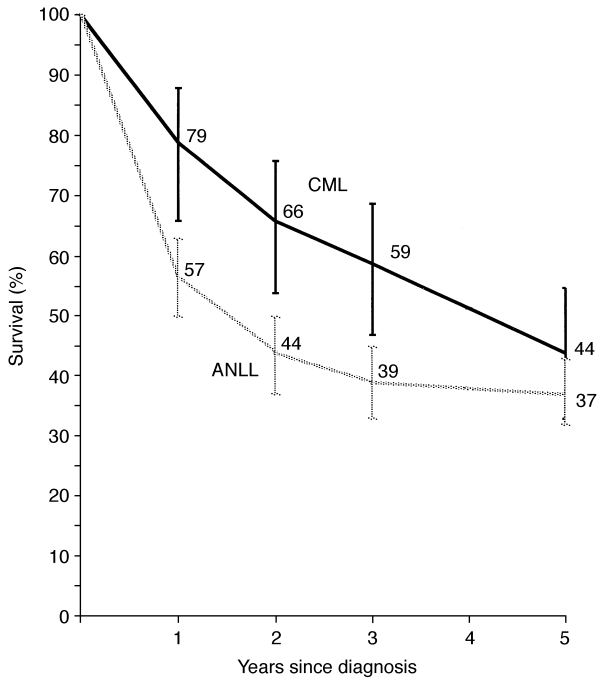

Fig. 1. Survival curves (with 95% CI) for ANLL and CML in Europe, children diagnosed 1985–1989 (from the European weighted pool). 95% CI, 95% confidence interval; CML, chronic myeloid leukaemia; ANLL, acute non-lymphocytic leukaemia.

CML declined steadily in the 5 years after diagnosis, from 79% at 1 year to 44% at 5 years.

3.1. Morphological sub-types

Table 2 shows the proportions and the numbers of cases of the various histological subtypes recognised by the ICCC [8]. Acute myeloid leukaemia (AML) is the most frequently cited (81.4%) subtype of ANLL, however AML includes several subtypes which are often labelled only as AML. The other most frequent ANLL subtypes are acute monocytic (8.5%) and promyelocytic (4.4%). For CML, the only subtypes usually recognised are chronic myeloid (89.2%) and chronic myelomonocytic (10.8%). Table 2 also shows 5-year survival for each subtype. The most favourable survival was for AML (42%; 95% CI 38–46) and acute promyelocytic leukaemia (48%; 95% CI 33–63), with monocytic leukaemia (35%; 95% CI 25–46), megakaryblastic leukaemia (27%; 95% CI 14–44) and erythroleukaemia (26%; 95% CI 12–49) having the worst prognoses. Only 1 case was labelled as myelomonocytic and 2 cases as erythremia and all three were dead within 5 years. Survival was similar for the two chronic myeloid forms.

3.2. Effect of gender and age on survival

Outcome for girls was better than for boys (Table 3). For ANLL, 5-year survival was 43% (95% CI 39–48) for girls and 37% (95% CI 32–41) for boys, although no major survival differences were seen for children diagnosed at age less than 5 years. For CML, survival at 5 years was 41% (95% CI 29–53) for girls and 30% (95% CI 21–40) for boys, the difference being mainly due to survival differences in children aged 10–14 years and in infants. Similar patterns were seen in the larger series for 1978–1989 (data not shown but the gender difference in survival for the different age groups was not always statistically significant.

For children with ANLL, 5-year survival was highest (48%; 95% CI 41–55) in the 5–9 year age class. For CML, the most favourable prognosis was for infants (51%; 95% CI 31–71), while children aged 1–4 years had the poorest outcome (15%; 95% CI 7–27).

3.3. Inter-country survival differences

Geographical differences in age-standardised survival for ANLL and CML at 1 and 5 years are shown in Table 4. For ANLL, Finland, the UK, The Netherlands, Germany and Italy had good survival at 1 year ($\geqslant$65%); survival was also good at 5 years ($\geqslant$40%) for these countries, except in Italy (38%; 95% CI 26–52). For CML, for which few countries could be compared

Table 3
5-year survival, with 95% CI for ANLL and CML in European[a] children, by age and gender[b,c]

	Age (years)				
	<1	1–4	5–9	10–14	All ages
ANLL					
Boys	36, 25–49 (59)	39, 32–47 (161)	42, 33–52 (96)	30, 23–38 (142)	37, 32–41 (458)
Girls	37, 25–51 (48)	37, 30–45 (155)	53, 44–62 (107)	45, 37–53 (147)	43, 39–48 (457)
CML					
Boys	41, 21–65 (16)	15, 6–31 (32)	50, 25–75 (12)	32, 18–52 (27)	30, 21–40 (87)
Girls	80, 38–96 (5)	14, 4–38 (18)	39, 20–61 (18)	55, 34–74 (20)	41, 29–53 (61)

ANLL, acute non-lymphocytic leukaemia; CML, chronic myeloid leukaemia.
[a] From the European unweighted pool.
[b] Cases diagnosed 1985–1989; number of cases in parentheses.
[c] Source of data EUROCARE.

Table 4
Age-standardised 1- and 5-year survival (%) with 95% CI for ANLL and CML by country, children diagnosed 1985–1989[a,b]

	(No. of cases)	Survival% at:	
		1 year	5 years
Acute non–lymphocytic leukaemia			
Finland	(29)	65 (46–81)	44 (28–61)
Sweden	(10)	30 (14–54)	23 (8–49)
Denmark	(31)	47 (30–66)	19 (8–39)
Scotland	(27)	67 (46–82)	50 (33–66)
England and Wales	(303)	60 (54–65)	42 (37–48)
The Netherlands	(82)	68 (57–78)	40 (30–51)
Germany	(283)	69 (63–74)	45 (40–51)
Italy	(47)	71 (57–82)	38 (26–52)
Spain	(19)	36 (19–57)	24 (9–48)
Slovenia	(12)	64 (37–84)	8 (1–35)
Slovakia	(38)	57 (41–73)	23 (12–41)
Europe[c]	(915)	57 (53–63)	38 (33–43)
Chronic Myeloid Leukaemia			
England and Wales	(46)	63 (49–75)	24 (14–39)
Germany	(55)	74 (62–84)	45 (32–58)
Italy	(8)	100 (100–100)	84 (22–99)
Slovakia	(12)	79 (33–96)	27 (9–57)
Europe[c]	(148)	81 (65–91)	46 (31–60)

ANLL, acute non-lymphocytic leukaemia; CML, chronic myeloid leukaemia.
[a] The national registries are in bold.
[b] Source of data: EUROCARE.
[c] The figure for Europe includes countries not shown in the table because of small numbers and it is weighted for the childhood population in each country.

because of the lack of cases, survival at 1 and 5 years was highest in Italy (100% 95% CI 100–100 and 84%; 95% CI 22–99). In Slovakia, survival was high at 1 year (79%; 95% CI 33–96) but had declined considerably at 5 years (27%; 95% CI 9–57).

3.4. Survival trends.

Survival for both kinds of childhood leukaemia improved considerably from 1978 to 1989. Table 5 shows the results of a Cox proportional regression analysis performed on data from those countries with data for the entire period, during which the risk of dying fell by 7 and 5% per year for ANLL and CML respectively, after adjustment for age, gender and country.

4. Discussion

A comparison of ANLL and CML 5-year survival rates in Europe with that in other industrialised countries is given in Table 6 [15–18]. European survival rates did not differ greatly from those in North America and Australia, but were clearly higher than in Japanese children. However, these comparisons are crude and a proper interpretation of the differences would require a thorough evaluation of data quality and age-standardisation. Overall, survival was generally better for CML than ANLL, except in Japanese children. This can be explained in terms of the natural history of the illness: in CML the cellular growth fraction is small, so that in the early years after diagnosis survival is better (see Fig. 1). By contrast, ANLL is faster growing, and more deaths occur within the first 2 years of diagnosis (479/915) than with CML (64/148).

This study shows that for ANLL and CML, survival was slightly better for girls than boys. For ANLL, this was the case for almost all the European countries individually (data not presented); a similar gender-related survival difference for ANLL is reported for US [15] and Japanese [16] children. The mechanisms by which gender may influence the growth and progression of these leukaemias are unknown. It is possible that female gender hormones and other gender-related factors may affect the natural killer cell activity or other host defence mechanisms [19]. This seems reasonable because gender-related survival differences are more marked in older

Table 5
Time trend (from 1978 to 1989) for survival of children with ANLL or CML. Cox proportional regression analysis[a,b,c]

Diagnostic group	(No. of cases)	Period of diagnosis	RR	(95% CI)	RR per year	(95% CI)
ANLL	(1811)	1978–1981	1			
		1982–1985	0.75	(0.65–0.86)	0.93	(0.91–0.95)
		1986–1989	0.57	(0.49–0.65)		
CML	(278)	1978–1981	1			
		1982–1985	0.77	(0.54–1.09)	0.95	(0.91–0.99)
		1986–1989	0.67	(0.48–0.94)		

ANLL, acute non-lymphocytic leukaemia; CML, chronic myeloid leukaemia.
[a] Countries included in the analysis are, for ANLL: Denmark, The Netherlands, England and Wales, Finland, Germany, Italy, Scotland and Slovakia; for CML The Netherlands, England and Wales, Germany, Scotland and Slovakia.
[b] Variables included in the model are gender, age, country* and period of diagnosis (the latter both as categorical and as a continuous variable).
[c] Source of data: EUROCARE.

Table 6
Comparison of 5-year survival for ANLL and CML in Europe, USA, Japan, Canada and Australia (population-based studies)[a]

	Europe		USA, all races	Osaka, Japan	Canada[b]	Victoria, Australia
	1978–1989	1985–1989	1978–1986	1980–1984	1985–1988	1980–1989
ANLL	29	37	23.6	24.9	39	41
CML	27	44	29.5	15.0	N/A[c]	46

Sources: Europe, EUROCARE Study; USA, SEER Program [14]; Japan, Osaka Cancer Registry [15]; National Cancer Incidence Reporting System [16]; Victoria Cancer Registry [17].

[b] Children aged 0–19 years.

[c] N/A, data not available.

children (Table 3). However, better survival in girls could also be due to a more favourable distribution of histological sub-types, within the broad category of ANLL not otherwise specified (NOS) (ICD-O code 9861).

It is noteworthy that diagnostic techniques were improving markedly during the period covered by study, especially for ANLL [20]. In particular, monoclonal antibodies became available which allowed immunological differentiation of haemopoietic cells, and more precise definition of new ANLL subtypes [21,22]. Immunophenotyping is particularly useful for distinguishing immature ANLL cells from immature ALL cells, for better defining the maturation block in various ANLL subtypes, and for identifying hybrid and bi-phenotypic leukaemias.

This study has also shown age-related variations in survival. The worst outcome was in infants with ANLL and in children aged 1–4 years with ANLL or CML. Similar findings for ANLL have been reported in Canadian and Australian children [17,18]. Difficulties in administering intensive and prolonged treatments to the youngest children, and the low probability of having, at that age, a sibling donor for allogeneic bone marrow transplantation may explain this. Gender- and age-related survival differences were also seen in the earlier and larger series of European children, diagnosed between 1978 and 1989 (used for the analysis of time trends in this study). For ANLL, Stiller [23] found that children less than 1 year of age had low survival rates and were less likely to have M2 leukaemia (myeloblastic with differentiation, FAB classification) with good prognosis. In the same study, children diagnosed with ANLL during the period 1971–1988 who also had Down's syndrome were more likely to be undertreated (61%) and also more often had cardiac abnormalities (87%); furthermore, ANLL cases with both conditions (Down's syndrome and cardiac abnormalities) were concentrated among infants (93%).

Even if improvement in survival for childhood ANLL and CML over time was not as remarkable as for acute lymphoblastic leukaemia (ALL), significant progress in survival for ANLL and CML occurred from the late 1970s with the introduction of polychemotherapy in that decade, and with the introduction in the following decade of new drugs and dose intensification regimens involving megatherapies and bone marrow transplantation. For ANLL, improvements in diagnostic classification based on immunology and cytogenetics enabled subgroups of patients with differing prognoses to be defined, making it possible to tailor the therapy and the intensity of treatment more precisely.

Because of the rarity of these diseases we used national registries, and grouped registries in Spain and Italy, to compare survival in different European populations. 5-year survival was better in Finland, the UK, Germany, The Netherlands and Italy, and relatively poor for the Eastern European countries and Spain. Variation in the extent of centralisation of treatment and the extent to which clinical trials were conducted have been proposed to explain these international differences [22]. It is important to note that, during the study period, some countries were setting up national networks for conducting large clinical trials, with the result that the resources devoted to paediatric oncology varied greatly from one country to another. Furthermore, paediatric oncologists were active in drawing up international guidelines for treatment in only some of the participating countries. It was not until the 1990s (after the period covered by this study) that the International Society of Paediatric Oncology (SIOP) issued guidelines for training paediatric oncologists and haematologists, and for the standard of care in paediatric cancer units.

Most of the registries considered in this survival comparison cover the entire populations of the countries concerned. They therefore give a good description of survival in those countries. This may not be the cases for Italy and Spain. In Italy, only 15.4% of the childhood population is covered by cancer registration; however, during the study period, seven out of nine Italian registry areas had specialised centres for paediatric oncology involved in the Italian National Association of Paediatric Haematology and Oncology (AIEOP) [24]. In these centres, the majority of children were treated in the context of clinical trials. This would explain the relatively good survival rates in children in the pooled Italian data.

For Spain, low survival rates were also reported by the Spanish National Childhood Tumour Registry [25], 5-year survival of children with 'other leukaemias' diagnosed in 1980–1989 was only 21%. This registry was not population-based, but probably included all cases treated by paediatric oncologists, so it is unlikely that survival was lower than in the national population.

For children diagnosed with ANLL in Britain in 1971–1988 [23], recruitment to national trials and treatment in teaching hospitals were associated with higher survival in an analysis which controlled for age at diagnosis, and where untreated children (12%) were excluded. Other causes of between-population differences in survival may be related to delayed presentation, which could in turn be due to deficiencies in primary care or health education. Differences in treatment could occur if children of a certain socio-economic status or in a given area of residence were more likely to be referred to a major treatment centre than other children [4]. Two major studies have investigated these factors in childhood leukaemia groups [26,27]. Coleman and colleagues investigated children with various cancers in England and Wales [26], and found that survival for all leukaemias was worse in the deprived group, but the differences were not significant. Coebergh and colleagues [27] investigated survival from childhood leukaemias in The Netherlands and also found minimal differences in survival in relation to parental education level.

This population study of survival from childhood ANLL and CML is the largest yet conducted. Such studies are vital for monitoring the effects on survival of new treatment protocols and new arrangements for the organisation of treatment. Since these are rare neoplasms, large databases such as EUROCARE are necessary to provide a reliable picture of survival trends. Improved survival for these malignancies may be expected from improvements in supportive care which limit the acute and late side-effects of potentially curative treatments, and also from the introduction of more effective and less toxic chemotherapy regimens. We hope that EUROCARE can be expanded in the future to include more childhood cancer registries, particularly in Spain, France and Switzerland, which were underrepresented in this study. EUROCARE should continue to study survival to verify that long-term remission can be obtained in these rare malignancies.

5. The EUROCARE Working Group for this study

Austria: W. Oberaigner (Cancer Registry of Tirol). *Denmark*: H. Storm (Danish Cancer Society 'Institute of Cancer Epidemiology'). *Estonia*: T. Aareleid (Estonian Cancer Registry). *Finland*: T. Hakulinen (Finnish Cancer Registry). *France*: J. Mace-Lesec'h (Calvados General Cancer Registry P.M. Carli (Côte d'Or Malignant Haemopathies Registry), P. Arveux (Doubs Cancer Registry), N. Raverdy (Somme Cancer Registry). *Germany*: P.Kaatsch, J. Michaelis (German Registry of Childhood Malignancies), *Iceland*: L. Tryggvadottir, H. Tulinius (Icelandic Cancer Registry). *Italy*: P. Crosignani (Lombardy Cancer Registry), E. Conti (Latina Cancer Registry), M. Vercelli (Liguria Cancer Registry — NCI, Genova), M. Federico, L. Mangone (Modena Cancer Registry), V. De Lisi (Parma Cancer Registry), C. Magnani (Piedmont Childhood Cancer Registry), L. Gafà, R. Tumino (Ragusa Cancer Registry), F. Falcini (Romagna Cancer Registry), A. Barchielli (Tuscan Cancer Registry), *Poland*: J. Pawlega, J. Rachtan (Cracow Cancer Registry), M. Bielska-Lasota, Z. Wronkowski (Warsaw Cancer Registry). *Slovakia*: A. Obsitnikova, I. Plesko (National Cancer Registry of Slovakia). *Slovenia*: V. Pompe-Kirn (Cancer Registry of Slovenia). *Spain*: I. Izarzugaza (Basque Country Cancer Registry), I. Garau (Mallorca Cancer Registry), E. Ardanaz, C. Moreno (Navarra Cancer Registry), J. Galceran (Tarragona Cancer Registry). *Sweden*: T. Möller (Southern Swedish Regional Tumour Registry). *Switzerland*: C. Bouchardy, L. Raymond (Geneva Cancer Registry). *The Netherlands*: A. Van Der Does-van der Berg (Dutch Childhood Leukaemia Study Group). *Scotland*: R. Black, A. Gould (Scottish Cancer Registry). *England and Wales*: CA Stiller (Childhood Cancer Research Group, Oxford).

Study Coordinator, Data Centre and Steering Committee: F. Berrino (Project Leader), G. Gatta, A. Micheli, M. Sant (Division of Epidemiology, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy), R. Capocaccia, M. Santiquilani, F. Valente, A. Verdecchia (Department of Epidemiology and Biostatistics, Istituto Superiore di Sanita, Rome, Italy), J.W. Coebergh (Eindhoven Cancer Registry), M.P. Coleman (London School of Hygiene and Tropical Medicine, London, UK), J. Estève (Service de Biostatistique, Centre Hospitalier Lyon Sud, France), J. Faivre (Cote d'Or Digestive Cancer Registry, Dijon, France), D. Forman (Northern and Yorkshire Cancer Registry and Information Service & Centre for Cancer Research), T. Hakulinen (Finnish Cancer Registry, Helsinki Finland), C. Martinez-Garcia (Granada Cancer Registry, Spain).

Acknowledgements

The EUROCARE study was financed through the BIOMED programme of the European Community. The authors are grateful to Charles Stiller, Benedetto Terracini and Guido Pastore for critically reading the manuscript and to Donald Ward for help with English. They are also indebted to Silvia Viscomi for her help in data analysis.

References

1. Parkin DM, Kramarova E, Draper GJ, *et al*., eds. *International Incidence of Childhood Cancer, Vol. II, IARC Scientific Publication No. 144*. Lyon, International Agency for Research on Cancer, 1998.
2. Ferlay J, Bray F, Sankila R, Parkin DM. *EUCAN Cancer Incidence, Mortality and Prevalence in the European Union*. Lyon, IARC Press, 1999.
3. Pui CH. Childhood leukemias. *New Engl J Med* 1995, **332**, 1618–1630.
4. Stiller C. Centralised treatment, entry to trials and survival. *Br J Cancer* 1994, **70**, 352–362.
5. Sanders J, Glader B, Cairo M, *et al*. Guidelines for the paediatric cancer center and role of such centers in diagnosis and treatment. American Academy of Pediatrics Section Statement on Hematology/Oncology. *Pediatrics* 1997, **99**(1), 139–141.
6. Magnani C, Gatta G, Corazziari I, *et al*. Childhood malignancies in the EUROCARE study: the database and the methods of survival analysis. *Eur J Cancer* 2001, **37**, 678–686.
7. Berrino F, Sant M, Verdecchia A, Capocaccia R, Hakulinen T, Estève J, eds. *Survival of Cancer Patients in Europe. Scientific Publication No., 132*. Lyon, International Agency for Research on Cancer (IARC), 1995.
8. Kramarowa E, Stiller CA. The International classification of childhood cancer. *Int J Cancer* 1996, **68**, 759–765.
9. Berrino F, Capocaccia R, Estève J, *et al*. *Survival of Cancer Patients in Europe: The EUROCARE Study-2. IARC Scientific Publication No 151*. Lyon, International Agency for Research on Cancer, 1999.
10. Coebergh J-W, Pastore G, Gatta G, Corazziari I, Kamps W and the EUROCARE Working Group. Variation in survival of European children with acute lymphoblastic leukaemia, diagnosed in 1978–1992: the EUROCARE study. *Eur J Cancer* 2001, **37**, 687–694.
11. Capocaccia R, Gatta G, Chessa E, the Eurocare Working GroupThe Eurocare-2 study. In Berrino F, Capocaccia R, Estève J, *et al*, eds. *Survival of Cancer Patients in Europe: the EUROCARE Study II. IARC Scientific Publication No. 151*. Lyon, International Agency for Research on Cancer, 1999.
12. Hakulinen T, Abeywickrama K. A computer program package for relative survival analysis. *Comp Prog Biomed* 1987, **19**, 197–207.
13. Verdecchia A, Capocaccia R, Santaquilani M, Hakulinen T. Methods of survival data analysis and presentation issues. In Berrino F, Capocaccia R, Estève J, *et al*., eds. *Survival of Cancer Patients in Europe: The EUROCARE Study II. IARC Scientific Publication No. 151*. Lyon, International Agency for Research on Cancer, 1999.
14. Cox D. Regression models and life tables. *J R Stat Soc B* 1972, **34**, 187–220.
15. Miller RW, Young JI, Novakovic B. Childhood Cancer. *Cancer* 1995, **75**, 395–405.
16. Ajiki W, Hanai A, Tsukuma H, Hiyama T, Fujimoto I. Survival rates of childhood cancer patients in Osaka, Japan, 1975–84. *Jpn J Cancer Res* 1995, **86**, 13–20.
17. Villenueve PJ, Sankaranarayanan R, Leclerc JM, Huchcroft S, Dryer D, Morrison H. Survival rates among Canadian children and teenagers with cancer diagnosed between 1985 and 1988. *Cancer, Prevention and Control* 1998, **2**(1), 15–22.
18. Giles G, Waters K, Thursfield V, Farrugia H. Childhood cancer in Victoria, Australia, 1970–1989. *Int J Cancer* 1995, **63**, 794–797.
19. Adami HO, Bergström R, Holmberg L, Klareskog L, Persson I, Pontén J. The effect of female sex hormones on cancer survival. *Jama* 1990, **263**, 2189–2193.
20. Bennett JM, Catovsky D, Daniel T, *et al*. Proposed revised criteria for the classification of the acute leukaemias. *Ann Int Med* 1985, **103**, 626.
21. San Miguel JM, Gonzalez M, Canizo MC, *et al*. Leukaemias with megakaryoblastic involvement: clinical, hematologic, and immunologic characteristics. *Blood* 1988, **72**, 402.
22. Cheson B, Cassileth P, Head D. Report of the National Cancer Institute-sponsored workshop on definitions of diagnosis and response in acute myeloid leukaemia. *J Clin Oncol* 1990, **8**, 813.
23. Stiller CA, Eatock EM. Survival from acute non-lymphocytic leukaemia, 1971–88: population based study. *Arch Dis Child* 1994, 219–223.
24. Pession A, Rondelli R, Haupt R, *et al*. Sistema di rilevazione dei casi di tumore maligno in età pediatrica in Italia su base ospedaliera. The Italian hospital-based registry of paediatric cancer. *Riv Ital Pediatr* 2000, **26**, 333–341.
25. Peris-Bonet R, Guiral Rodrigo S, Melchor Alos I. Registro Nacional de Tumores Infantiles. Estadisticas Basicas 3 (1980–1990). Supervivencia (1980–1989). Valencia, Conselleria de Sanitat i Consum.
26. Coleman MP, Babb P, Damiecki P, *et al*., eds. *Cancer Survival Trends in England and Wales 1971–1995: Deprivation and NHS Region*. London, Office for National Statistics, The Stationery Office, 1999.
27. Coebergh JWW, van Does-van den Berg A, Hop WCJ, van Weerden F, *et al*. Small influence of parental educational level on the survival of children with leukaemia in The Netherlands between 1973 and 1979. *Eur J Cancer* 1996, **32A**, 286–289.