Adolescents and young adults with acute lymphoblastic leukaemia: A new frontier?

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The word adolescent derives from the Latin *adolescere*, which means 'to grow'. There is no agreed precise definition of adolescence or young adulthood. Some dictionaries define adolescence arbitrarily as 'around 12–18 years in girls and 14–20 years in boys'. The Anglo-Saxon word 'teenager' encompasses the period from 13 to 19 years. The World Health Organisation (WHO) definition[1] considers adolescents to be individuals aged 10–19 years. Whatever the exact definition, adolescents with cancer or leukaemia are treated either by paediatric haemato-oncologists, or by adult haematologists or oncologists. Young adults are treated by the latter. The concept of adolescents and young adults has emerged recently in the field of cancer, particularly in acute lymphoblastic leukaemia (ALL), which is the focus of this review.

Cancer in adolescents: facts and general comments regarding their treatment

Cancer is the leading cause of non-accidental death in children and adolescents under the age of 20 years [1]. In this age range, one-third of cases involve adolescents between 15 and 20 years of age [1,2]. Hodgkin's and non-Hodgkin's lymphomas account for 25% of the tumours. Leukaemias represent only 15% of all the tumours, compared with 30% prior to 10 years of age. ALL and acute myeloid leukaemia (AML) represent 65% and 35%, respectively, of all acute leukaemias observed in the 15–20 years population versus 85% and 15%, respectively, in children under 15 years of age [2]. A small increase in cancers in this age range has been found in industrialised countries, essentially due to an apparent increase in ALLs [1].

Two questions are of particular importance in considering the subject of adolescents with cancer: Do they benefit from the most adapted therapies? And how can levels of compliance be improved?

Do adolescents benefit from the most adapted therapies?

Hemato-Oncology co-operative groups offer the best therapeutic options. This is demonstrated particularly in the paediatric setting [3]. One epidemiological problem is that only the patients included in protocols are registered. A large study in the United States of America (USA) has shown that 97.6% of the children aged 15 years or less are registered in Pediatric Oncology protocols, compared with only 21% of the adolescents aged 16–21 years [4]. In the latter category, less than 3% are registered in adult haematology or oncology protocols [4,5]. Potential explanations are numerous, but this leads to the conclusion that a great part of the adolescent population is treated suboptimally, outside paediatric or adult haemato-oncology networks. Even though these numbers probably do not represent the European reality, the same conclusion is at least partially applicable. A comparison of adult and paediatric therapeutic strategies is detailed below.

1.2. Compliance and adolescents

One of the general problems encountered in treating a severe disease in an adolescent population is diminished compliance with treatment. Some studies have documented this notion, sometimes by measuring the urinary or serum level of the prescribed drugs. Festa and colleagues have thus evaluated compliance with prednisone treatment in adolescents treated for ALL and Hodgkin's disease: 52% of the patients were considered to be non-adherent to the treatment [6]. A nationwide study in the United Kingdom (UK) of intracellular drug metabolite concentrations in 496 children who had been prescribed 6-mercaptopurine for the treatment of ALL was carried out to assess inter-patient variability at a standardised dose. Nine

[1] 1986; http://whqlibdoc.who.int/trs/WHO_TRS_731_fre.pdf

children (2% of the total) had completely undetectable metabolites, indicative of complete non-compliance, five of whom were adolescents [7]. Numerous factors seem to influence compliance, including socio-economic status, comprehension of the mode of drug administration, ease of drug availability, clear definition of the responsibilities of the adolescent and his or her parents, and the number of children in the family [8]. Further research is required on this subject.

Acute lymphoblastic leukaemia in adolescents

Prognostic parameters

Five-year event-free survival (EFS) of children with ALL is now approaching 80% [9]. Age is a well-known prognostic variable. A classic age limit is set at 10 years, as used in the Rome–National Cancer Institute (NCI) classification [10]. Nevertheless, this limit is rather 'fuzzy', some teams finding a worst prognosis after 6 or 7 years [11,12], other groups considering a limit of 11 years as relevant [13]. In fact it seems that after the peak of common ALL a progressive decrease in the prognosis is observed, leading to the dismal prognosis of adult ALL (approximately 30–40% cure rate) [14].

Adolescents over 15 years of age have been known to have a poorer prognosis, resembling the one of young adults, in terms of obtaining a complete remission (CR) [13] or disease-free survival (DFS) duration [13–16]. Two studies from the Memphis group, performed in the 1980s, showed a significant difference in outcome between the children aged from 10 to 15 years and adolescents above 15 years [15,16]. The current view is that this is now not the case, as demonstrated by several recent studies, favouring the idea that adolescence begins at 10 years in ALL. A Children's Cancer Group study shows identical EFS for the two subpopulations, but inferior EFS to the one in those patients under 10 years old [17]. The same observation has been made for patients treated within the French Acute Lymphoblastic Leukaemia Group (FRALLE) 93 protocol (data on file). A study from the Dana Farber Cancer Institute conducted between 1991 and 2000 has been published recently [18]. The authors compared the outcomes in three age groups: children aged 1–10 years ($n = 685$), young adolescents aged 10–15 years ($n = 108$), and older adolescents aged 15–18 years ($n = 51$). With a median follow-up of 6.5 years, the 5-year EFS for those aged 1–10 years was 85% (standard error (SE) 1%), compared with 77% (SE 4%) for those aged 10–15 years, and 78% (SE, 6%) for those aged 15–18 years ($P = 0.09$) [18]. Reasons associated with a worse prognosis in adolescents are multifactorial.

Factors linked to the patient

More boys than girls are encountered in this group, male gender being associated with a worse prognosis. The pharmacological characteristics of this population are not well known. Nevertheless, the toxicity of some major drugs for ALL is augmented, leading to dose reduction. For example, adolescents have a diminished clearance of vincristine compared with younger children (under 10 years of age), explaining the neurotoxicities observed [19]. A greater frequency of avascular necrosis is encountered with dexamethasone. Burger and colleagues retrospectively analysed 1951 patients under 18 years of age, who were treated according to trial ALL-BFM 95 between 1996 and 2000. The overall 5-year cumulative incidence for avascular necrosis is 1.8%. The incidence for patients <10 years is 0.2%, whereas for patients $\geqslant 10$ years it is 8.9% ($P = 0.001$) and for patients $\geqslant 15$ years and less than 19 years it is 16.7% ($P = 0.003$) [20]. A higher risk of central nervous system (CNS) thrombosis linked to L-asparaginase has been suggested in girls using contraception.

Reduced compliance is likely to interfere with the intensity of oral maintenance treatment with mercaptopurine and methotrexate, the paramount importance of which has been well-established [21].

Features linked to the disease

Beyond the age of 10 years are encountered ALLs carrying a higher risk of treatment failure. A summary of these features is given in Table 1 [13,15–18]. A clear increase in the T-cell ALL frequency is documented (less than 15% under 15 years of age compared with 25–30% above this age), a feature associated with a

Table 1
Biological features often encountered in adolescents with acute lymphoblastic leukaemia (ALL)

WBC count > 50,000/mm^3
Elevated LDH
T-cell ALL
B-lineage CD10-negative ALL
Low incidence of hyperdiploidy
Very low incidence of t(12;21)/TEL-AML1 positive ALL
Slight increase in Philadelphia-positive ALL
Poor early response to prednisone

WBC, white blood cell; LDH, lactate dehydrogenase

higher risk of failure. A cohort of 258 adolescents (15–20 years old) were treated in the successive FRALLE 83, FRALLE 87–89, FRALLE 92 (pilot phase), FRALLE 93 and FRALLE 2000 protocols (Baruchel ASH 06). The main characteristics were: a sex ratio of 1.8 (M/F), a B-lineage in 71% of cases versus T-lineage in 29% of patients aged 15–20 years between 1987 and 1999 with 27% of T-ALL (Baruchel ASH 06). Nachman and colleagues report a 21% incidence in 143 adolescents aged 16–21 years [17]. These numbers are the same as those encountered in the adult population [14]. A progressive increase in B-lineage Philadelphia chromosome positive ALL, associated with a dismal prognosis has been reported after the age of 15 years, and particularly over the age of 20 years. No such an observation has been made in the FRALLE/Leucémies Aigues Lymphoblastiques de l'Adulte (LALA) study, described below, on 177 patients aged 15–20 years (incidence: 2.5%) [22].

A lower incidence of forms associated with a good outcome is observed in that population: incidence of hyperdiploidy is reduced [13,15,16]. The frequency of hyperdiploidy more than 50 chromosomes was 16% in the recent FRALLE/LALA study, an intermediate value between the 25% observed in children and the 5% displayed by adults [22]. Only rare forms with TEL-AML1 leukaemia are observed above the age of 10 years. This cryptic t(12;21) rearrangement, observed in about 20% of cases of childhood ALL, but in less than 2% of cases of adult ALL, was present in 7% of adolescents in the FRALLE-93 trial [22]. Even if a rare event in childhood, ALL (2%) amplification of the long arm of chromosome 21 is more frequent in older children and adolescents and seems to be associated with a worse prognosis [23,24].

The cytogenetic 'black hole', at the frontier between adult and childhood populations, suggests the existence of unknown factors to explain the worse prognosis of adolescents among children. It is hoped that current studies on expression or proteomics profiles will throw light on this issue.

Several studies have also reported differences in ALL cell sensitivity to corticosteroids and chemotherapy *in vitro* [25,26]. No study detailing the early response in term of minimal residual disease is yet available in this population.

2.2. Paediatric or adult protocols?

It is a fact that adolescents, considered as high-risk patients by paediatricians, are considered as good risk patients when evaluated by adult haematologists. Paediatric protocols, which are generally much more intensive than adult protocols, give the best outcome, even if all the comparative studies are retrospective. After the first fully reported French study [22], numerous abstracts and articles have confirmed that notion. They are summarised in Table 2 [27–32].

We focus here on the French report, which is still the most detailed and which was the only one to include all the individual data in the same database, allowing multivariate analysis [22]. From June 1993 and September 1994, 77 and 100 evaluable adolescents ($\geqslant$15 years, <20 years) were enrolled in the paediatric FRALLE-93 and adult LALA-94 protocols. Among the different prognostic factors, the trial was analysed for probability of achieving complete remission or EFS. Patients were younger in the FRALLE-93 (median age: 15.9 versus 17.9) but other characteristics were similar: median WBC (18 versus 16×10^9/l), B/T-lineage (54/23 versus 72/28), CD10-negative (13% versus 15%), poor-risk cytogenetics (t(9;22), t(4;11), hypodiploidy <45 chromosomes; 6% versus 5%). The CR rate depended on the white blood cell (WBC) count ($P = 0.005$) and the trial (94% versus 83%; $P = 0.04$). Univariate analysis showed that unfavourable prognostic factors for EFS were the WBC count ($P < 0.0001$), the trial (estimated 5-year EFS 67% versus 35%; $P < 0.0001$), T-lineage ($P = 0.01$) and cytogenetics ($P = 0.01$). Trial and WBC count remained significant parameters for EFS in multivariate analysis ($P < 0.0001$). Significant differences within the B-Cell-Precursor-ALL subgroup were also observed for achieving CR (98% versus 81%; $P = 0.002$) and EFS ($P = 0.0002$), and within the T-ALL subgroup for EFS ($P = 0.05$) in favour of the paediatric protocol. Age was not a significant prognostic factor in that population. The same feature was found in a previous study of 143 adolescents aged 16–21 years from the Children's Cancer Group, in which EFS for patients aged 16–17, 18–19 and 20 years did not differ significantly [17]. Disparities in drug administration and dose-intensity between protocols were used to explain these differences in outcome. Differences in induction courses, which could underlie the observed gain in CR rates, are essentially: (i) the continuous administration of higher doses of prednisone; and (ii) the use of L-asparaginase in the FRALLE-93 protocol. Few pharmacological data are available to explain further this difference in remission rates. However, the three times daily administration schedule of steroids was shown to be superior to a more spaced administration in paediatric ALL [34]. Moreover, a study by the Dana-Farber Cancer Institute demonstrated an improved response to increased dose of steroids in patients aged 1–18

Table 2
Comparison of paediatric and adult trials including adolescents in their study population (modified and actualised from Ramanujachar and colleagues [33])

Trial	Years	Age range (yrs)	Adolescent age range (yrs)	*n*	CR rate (%)	EFS	DFS	OS
FRALLE 83	1983–87	0–20	15–20	48	89		47.5 (6 yrs)	
LALA 85	1985–	15–60	15–20	31	87		32 (4 yrs)	
FRALLE 93	1993–99	0–20	15–20	77	94	67 (5 yrs)	72 (5 yrs)	78 (5 yrs)
LALA 94	1994–2000	15–adult	15–20	100	83	41 (5 yrs)	49 (5 yrs)	45 (5 yrs)
CCG 1800 series	1989–95	0–21	16–21	196	96	64 (6 yrs)		
CALGB	1988–98	16–adult	16–21	103	93	38 (6 yrs)		
AIEOP ALL 95, 2000	1996–2003	0–18	14–18	150	94			80 (2 yrs)
GIMEMA ALL 0496, 2000	1996–2003	14–adult	14–18	95	89			71 (2 yrs)
DCOG 6–9	1985–99	0–18	15–18	47	98	69 (5 yrs)	71 (5 yrs)	
HOVON ALL-5, 18	1985–99	15–adult	15–18	44	91	34 (5 yrs)	37 (5 yrs)	
NOPHO	1992–2000	0–18	15–20	36	99	74 (5 yrs)		
SAALLG	1994–2000	15–40	15–20	23	90	39 (5 yrs)		
MRC ALL97/99	1997–2002	0–17	15–17	61	98	65 (5 yrs)		71 (5 yrs)
UKALL XII/E2993	1997–2002	15–55	15–17	67	94	49 (5 yrs)		56 (5 yrs)

CR, complete remission after induction; EFS, event-free survival; DFS, disease-free survival; OS, overall survival; FRALLE, FRench Acute Lymphoblastic LEukemia group; LALA, Leucémies Aigues Lymphoblastiques de l'Adulte; CCG, Children's Cancer Group; CALGB, Cancer and Leukemia Group B; AIEOP, Associazone Italiana Ematologia ed Oncologia Pediatrica; GIMEMA, Grupo Italiano Malattie Ematologiche Maligne dell Adulte; DCOG, Dutch Childhood Oncology Group; HOVON, Dutch-Belgian Hemato-Oncology Cooperative Study Group; NOPHO, Nordic Society of Pediatric Hematology and Oncology; SAALLG, Swedish Adult ALL Group; MRC, Medical Research Council; UKALL, United Kingdom ALL study group.

years [35]. Considering entire protocol periods, higher doses of major drugs in the treatment of ALL were used in the paediatric protocol, within a shorter period of time (3 times more vincristine, 5 times more prednisone, 20 times more L-asparaginase in 26 months versus 30 months). In the recent study of the Dana-Farber Consortium, children aged 9–18 years may benefit from higher doses of L-asparaginase despite an increased related toxicity [36]. In patients with T-ALL, repeated doses of L-asparaginase during early treatment significantly improved outcome in a randomised study of the Pediatric Oncology Group [37]. Moreover, the paediatric delayed intensifications may contribute to improve outcome. This strategy, initially proposed by the Berlin-Frankfurt-Munster study group [38] has been demonstrated by the Children's Cancer Group Study in children older than 10 years [39], with increased benefit of an augmented therapy including a double delayed intensifications in slow early responder patients [40].

Finally, therapeutic attitudes can interfere with the concept of dose-intensity [41]. Intervals between CR date time and day 1 of the first post-remission course were significantly longer in patients treated in the adult LALA-94 protocol, suggesting that dose-intensity could also be modulated by the usual inclination of physicians in adult centres to give patients time 'to get their breath back'.

Conclusion

The currently available comparative data encourage the inclusion of adolescents in intensive paediatric protocols and the design of new trials, inspired of paediatric protocols, for the treatment of younger adults with ALL. Immediate and long-term toxicity must be evaluated carefully and prospectively. Nevertheless, the toxicity profile of the paediatric approach is also likely to be inferior to that of currently available adult protocols, which make greater use of bone marrow transplantation in first CR.

It can be also recommended that only those physicians who are trained in the complexities of the intensive management of ALL and participation in co-operative studies should be involved in the care of adolescents and young adults with this rare disease.

Conflict of interest statement

None declared.

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