Paediatric Regimens for Adolescent & Young Adults

Abstract

The problem of the management of adolescents and young adults (AYA) with acute lymphoblastic leukemia (ALL) has progressively emerged, mainly in the last ten years. After recognizing that the biology disease was not identical to childhood ALL, pediatric investigators have focussed their efforts in two directions: intensification of the treatment and comparison of their results with adult protocols. This fruitful collaboration has led to the firm conclusion that the more intensive pediatric protocols were also more effective despite indicating less bone marrow transplantations. The results were so appealing that either "pediatric inspired " or pediatric protocols including patients until adulthood have been generated with promising results. More biology is still needed to understand differences with childhood ALL. More clinical research is still needed to prevent short term and long term toxic events in AYA.

Introduction

The word adolescent derives from the Latin *adolescere*, which means ‘to grow’. Not surprisingly, there is thus no 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 (1986; http://whqlibdoc.who.int/trs/WHO_TRS_731_fre.pdf) considers adolescents to be individuals aged 10–19 years.

Whatever the exact definition, adolescents with cancer or leukaemia are treated either by paediatric hemato-oncologists, or by adult haematologists or oncologists. Young adults are treated by the latters. The concept of adolescents and young adults (AYA) has emerged recently in the field of cancer, particularly in acute lymphoblastic leukaemia (ALL).

1. 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. In this age range, one-third of cases involve adolescents between 15 and 20 years of age. Hodgkin’s and non-Hodgkin’s lymphomas account for 25% of the tumours. Leukemias 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 leukemias observed in the 15–20 years population versus 85% and 15%, respectively, in children under 15 years of age. A small increase in cancers in this age range has been found in industrialised countries, essentially due to an apparent increase in ALLs.

1.1. 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. 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. In the latter category, less than 3% are registered in adult haematology or oncology protocols. 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 haematology-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 in ALL will be detailed in paragraph 2.2.

1.2. Compliance and adolescents

One of the general problems encountered in treating a severe disease in an adolescent population is the diminished compliance to 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. 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 children (2% of the total) had completely undetectable metabolites, indicative of complete non-compliance, five of whom were adolescents. Numerous factors seem to influence compliance, including socio-economic status, comprehension of the mode of drug administration, easiness of drug availability, clear definition of the responsibilities of the adolescent and his or her parents, and the number of children in the family. Further research on this subject is underway.

2. Acute lymphoblastic leukaemia in adolescents

2.1. Prognostic parameters

Five-year event-free survival (EFS) of children with ALL is now exceeding 80%. 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. Nevertheless, this limit is rather ‘fuzzy’, some teams finding a worst prognosis after 6 or 7 years, other groups considering a limit of 11 years as relevant. In fact it seems that after the peak of common ALL a progressive decrease in the prognosis is observed, leading to the worst prognosis of adult ALL (approximately 30–60% cure rate).

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) or disease-free survival (DFS) duration. 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. 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. The same observation has been made for patients treated within the French Acute Lymphoblastic Leukaemia Group (FRALLE) 93 protocol (5y EFS of the 10-14: 64±6% vs 68±11% for the 15-19, p=NS). The BFM group also made the same observation, particularly in the B-lineage ALLs (10y EFS of the 10-14: 60.6±2.9% vs 63.7±5.3% for the 15-18, p=NS). A study from the Dana Farber Cancer Institute conducted between 1991 and 2000 has also been published recently. 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).

Reasons associated with a worse prognosis in adolescents are multifactorial:

2.1.1. 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. A greater frequency
of avascular necrosis (AVN) 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 AVN is 1.8%. The incidence for patients < 10 years is 0.2%, whereas for patients = 10 years it is 8.9% \( (P = 0.001) \) and for patients = 15 years and less than 19 years it is 16.7% \( (P = 0.003) \). Similarly, in the recently published CCG 1961 study a 19.9% incidence has been reported for the 16-21 year-old age group\(^2\). 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 mercapto-purine and methotrexate, the paramount importance of which has been well-established\(^3\).

### 2.1.2. 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.

<table>
<thead>
<tr>
<th>Table 1. Biological features often encountered in adolescents with acute lymphoblastic leukaemia (ALL)</th>
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</thead>
<tbody>
<tr>
<td>WBC count &gt; 50,000 /mm(^3)</td>
</tr>
<tr>
<td>Elevated LDH</td>
</tr>
<tr>
<td>T-cell ALL</td>
</tr>
<tr>
<td>B-lineage CD10-negative ALL</td>
</tr>
<tr>
<td>Low incidence of hyperdiploidy</td>
</tr>
<tr>
<td>Very low incidence of t(12;21)/TEL-AML1 positive ALL</td>
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<tr>
<td>Slight increase in Philadelphia-positive ALL</td>
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<tr>
<td>Increased deletions/mutations of IKZF1?</td>
</tr>
<tr>
<td>Increased overexpression of CRLF2?</td>
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<tr>
<td>Poor early response to prednisone</td>
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</table>

WBC, white blood cell; LDH, lactate dehydrogenase;

A clear increase in the T-cell ALL frequency is documented (less than 15% under 15 years of age compared with 20–30% above this age), a feature associated to a 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 observation has been made in the FRALLE/LALA study, described below, on 177 patients aged 15–20 years (incidence: 2.5%)\(^2\).

A lower incidence of forms associated with a good outcome is observed in that population: incidence of hyperdiploidy is reduced\(^15,15,16\). 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\(^24\). 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\(^24\). Even if a rare event in childhood, ALL (2-3%) 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\textsuperscript{25, 26}. Finally the contribution of the recently described IKZF1 deletions/mutations and CRLF2 overexpression to the worse prognosis of adolescents is to be exactly quantified\textsuperscript{27, 28}.

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 genomics or proteomics will throw light on this issue.

Several studies have also reported differences in ALL cell sensitivity to corticosteroids and chemotherapy \textit{in vitro} \textsuperscript{29, 30}. No study detailing the early response in term of minimal residual disease and according to lineage is yet available in this population.

Table 2. Comparison of paediatric and adult trials including adolescents in their study population (modified and actualised from Ramanujachar and colleagues\textsuperscript{45})

<table>
<thead>
<tr>
<th>Trial</th>
<th>Years</th>
<th>Age range (years)</th>
<th>Adolescent age range (years)</th>
<th>n</th>
<th>CR rate (%)</th>
<th>EFS</th>
<th>DFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRALLE 83, LALA 85</td>
<td>1983–87, 1985–88</td>
<td>0–20, 15–60</td>
<td>15–20</td>
<td>48</td>
<td>89</td>
<td>–</td>
<td>47.5 (6 years)</td>
<td>–</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>15–20</td>
<td>31</td>
<td>87</td>
<td>–</td>
<td>32 (4 years)</td>
<td>–</td>
</tr>
<tr>
<td>FRALLE 93, LALA 94</td>
<td>1993–99, 1994–2000</td>
<td>0–20, 15–adult</td>
<td>15–20</td>
<td>77</td>
<td>94</td>
<td>67 (5 years)</td>
<td>72 (5 years)</td>
<td>78 (5 years)</td>
</tr>
<tr>
<td>CCG 1882, 1901</td>
<td>1989–95, 1988–98</td>
<td>0–21, 16–adult</td>
<td>16–20</td>
<td>197</td>
<td>90</td>
<td>63 (7 years)</td>
<td>41 (5 years)</td>
<td>45 (5 years)</td>
</tr>
<tr>
<td>AIIEP ALL 95, 2000</td>
<td>1996–2003</td>
<td>0–18, 14–18</td>
<td>14–18</td>
<td>150</td>
<td>94</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>GIMEMA ALL 0496, 2000</td>
<td>1996–2003</td>
<td>0–18, 14–adult</td>
<td>14–18</td>
<td>95</td>
<td>89</td>
<td>–</td>
<td>–</td>
<td>80 (2 years)</td>
</tr>
<tr>
<td>DCOG 6-9, HOVON ALL 5, 18</td>
<td>1985–99, 1994–2000</td>
<td>0–18, 15–15</td>
<td>15–18</td>
<td>47</td>
<td>98</td>
<td>69 (5 years)</td>
<td>34 (5 years)</td>
<td>71 (5 years)</td>
</tr>
<tr>
<td>NPHO saALLG</td>
<td>1992–2000</td>
<td>0–18, 15–40</td>
<td>15–20</td>
<td>36</td>
<td>99</td>
<td>74 (5 years)</td>
<td>39 (5 years)</td>
<td>–</td>
</tr>
</tbody>
</table>

CR, complete remission after induction; EFS, event-free survival; DFS, disease-free survival; OS, overall survival; FRALLE, FRench Acute Lymphoblastic LEukemia group; LALA, Leucémiés Aigües Lymphoblastiques de l’Enfant; CCG, Children’s Cancer Group; CALGB, Cancer and Leukemia Group B; AIIEP, Associazione Italiana Ematologia ed Oncologia Pediatrica; GIMEMA, Gruppo Italiano Malattie Eematologiche Maligne dell’Adulti; 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.

We will first focus on the French report which was the only one to include all the individual data in the same database, allowing multivariate analysis\textsuperscript{24}. From June 1993 and September 1994, 77 and 100 evaluable adolescents (\(<\) 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 looked for 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 [38]. Moreover, a study by the Dana-Farber Cancer Institute demonstrated an improved response to increased dose of steroids in patients aged 1–18 years [39]. Considering 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 [40]. 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 [41].

The US report has compared data in the 16-20 age range from the CCG studies (197 pts, studies 1882 and 1901, 1989-95) and the CALGB studies (124 pts, 5 studies, 1988-2001) [33]. The authors also found a difference in the median age (16 vs 19 years), meaning that the youngest patients were more likely to be treated in pediatric institutions. The 7-year EFS was also in favour of the pediatric protocols: 63% vs 34% overall even if an age effect was found for the patients treated in the CALGB studies with a better prognosis for the 16-17 compared to the 18-20 [33].

Moreover, the paediatric delayed intensifications may contribute to improve outcome. The efficacy of this strategy, initially proposed by the Berlin-Frankfurt-Munster study group [42] has been confirmed by the Children’s Cancer Group Study in children older than 10 years [43], with increased benefit of an augmented therapy including a double delayed intensifications in slow early responder patients [44]. The further intensification of the consolidation done in the CCG 1961 was proven to benefit to D7 rapid early responders: 5-year EFS of 81.8% (SE, 7%) vs 66.8% (SE, 6.7%) for standard therapy [22].

Finally, therapeutic attitudes can interfere with the concept of dose-intensity. 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’.

3. Conclusion

The currently available comparative data encourage the inclusion of AYA in intensive paediatric protocols and the design of new trials, inspired of paediatric protocols, for the treatment of younger adults with ALL as recently proposed [46-48]. These protocols should include all modern stratifiers for therapeutics including MRD studies.

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.

Acknowledgments: Marie-Françoise Auclerc, Nicolas Boissel, Sylvie Chevret

Conflict of interest statement

None declared.

References


25. Soulier J, Trakhtenbrot L, Najfeld V et al. Amplification of band q22 of chromosome 21, including AML1, in older children with acute lymphoblastic leukaemia: an emerging


