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Who should be treating adolescents and young adults with acute lymphoblastic leukaemia?

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Abstract

Although several cancers have a peak incidence during adolescence and young adulthood, the patients in this age group are arbitrarily referred to either paediatric or adult oncologists and, consequently, treated on different protocols. Recent reports show that paediatric oncologists are more likely to enroll patients in clinical trials, and that adolescents who are treated on paediatric protocols have a better outcome than their counterparts who are managed by adult oncologists. These observations were also noted in adolescents with acute lymphoblastic leukaemia (ALL), a disease with a bimodal peak incidence in early childhood and late adulthood. Recently, investigators have become aware that patients in the adolescent and young adult age group might be falling through the cracks because of the rigid organisation of the medical care system. In this article, I present some of the current challenges in the treatment of ALL in adolescents and young adults and propose strategies to improve outcome in these patients.
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1. Introduction

Referral patterns allow for cancer patients 13–21 years of age to be treated either by paediatric or by adult oncologists. Thus, 2 16-year-old patients with the same disease who are referred to the same cancer centre may well receive different protocols if one is referred to paediatrics and the other to adult services. Lately, efforts have been made to design combined paediatric/adult protocols for diseases like Hodgkin's lymphoma and osteosarcoma that have a peak incidence in the adolescent and young adult (AYA) age group. This strategy should also apply to leukaemia. ALL is a heterogeneous disease with a bimodal age distribution—an early peak between 2 and 6 years of age and a second peak in patients over 40 years. Younger children and older adults therefore constitute most of the 2500 children and 2000 adults diagnosed with ALL in the United States of America (USA) every year. Although 80% of children are cured with current ALL regimens [1, 2], less then 40% of adults with ALL are long-term survivors, despite implementation of treatment strategies that have proved successful in children [3–4]. Moreover, although adolescents and young adults tolerate and respond to current therapies better than older patients, their prognosis is not as good as children with leukaemia. Possible reasons for these discrepancies will be presented in this article along with suggestions for future strategies.

2. What makes adolescents and young adults different?

An understanding of the factors influencing ALL outcome in the AYA age group is needed to improve on current therapeutic strategies. Different factors—among them the disease itself, the host and the treatment—contribute to the inferior outcome in AYA compared with younger children.

2.1. Disease biology

Most children have prognostically 'favourable' ALL subtypes, but the incidence of 'unfavourable' characteristics increases gradually with age (Table 1). Hyperdiploidy

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Table 1
ALL characteristics in paediatrics and adults

Variable	Paediatric	Adult
Favourable		
% CALLA[a]	75	50
% hyperdiploid >50	20–30	<5
% t (12; 21)	20–30	<2
Unfavourable		
% t (9; 22)	<5	20–30
% 11q23	2[b]	6

ALL, acute lymphoblastic leukaemia.
[a] CALLA, common ALL antigen.
[b] Excluding infants <1 year old.

>50, trisomy of chromosomes 4, 10 and 17, and t (12; 21), occur mainly in 1–9-year-old children and are associated with a very low risk of treatment failure [5]. Paediatric ALL cells are more sensitive to prednisone, L-asparaginase, and vincristine than are adult ALL cells [6], which is reflected by the better response of children to induction therapy. Over half of adults with ALL have unfavourable pseudodiploidy [7]. The Philadelphia (Ph) chromosome, t(9;22), is the most frequent clonal abnormality in adult ALL, occurring in about 25% of cases. Less than 5% of children with ALL are Ph-positive; they are more likely to be older and to have a higher incidence of leucocytosis and involvement of the central nervous system (CNS) at diagnosis. Although t(9;22) is associated with a poor outcome in both children and adults, some children are long-term survivors, whereas this is an extremely rare event in adults [8,9].

MLL gene rearrangement, caused by translocations involving 11q23 and another genetic abnormality associated with a poor prognosis, occurs in 70–80% of children younger than 1 year and accounts for the dismal prognosis for infants with ALL. In all age groups, this translocation is associated with hyperleucocytosis, and a CD10-negative B-precursor phenotype. This type of poor prognosis MLL rearrangement is more common in adults than in children >1 year of age [10,11].

2.2. Host factors

Age is one of the most powerful predictors of treatment outcome in both paediatric and adult studies [12]. An important factor in determining outcome is the patient's ability to tolerate treatment. Organ function deteriorates with age, resulting in age-related differences in the metabolism of chemotherapeutic agents. Therefore, older patients generally have a depleted marrow reserve and increased extramedullary toxicity, making them prone to life-threatening infections, organ failure, treatment delays, and reductions in chemotherapy doses[1] [3,13]. Individuals also vary in their processing of antimetabolites such as methotrexate and 6-mercaptopurine. The favourable prognosis for children with hyperdiploid B-cell precursor ALL treated with antimetabolite-based therapy may be explained by the high capacity of hyperdiploid common ALL cells for polyglutamation of methotrexate [14–16]. Another potential explanation for the worse outcome in older patients with ALL may be related to the expression of the multidrug resistance (MDR1)-associated membrane protein (p170). Increased MDR1 expression in older patients is associated with resistance to anthracyclines, epidophyllotoxins, vinca alkaloids, and some alkylating agents [17,18].

2.3. Treatment differences

Chemotherapy selection, dose schedule, route of administration, drug metabolism, and compliance with the treatment plan all influence the probability of cure in leukaemia. ALL regimens are complex and are delivered over a 2–3 year period. ALL is the most common paediatric cancer, making most paediatric oncologists expert in the delivery of treatment and the management of side-effects. Children are more likely to be treated at large tertiary centres and to be followed more closely by primary physicians who follow the treatment plan with intense precision. By contrast, a considerable number of adults with ALL in the USA are seen in non-university settings, treated by physicians and support teams that see few leukaemia cases and are expert in the treatment of solid tumours rather than haematological malignancies [19]. Better disease-free survival (DFS) rates have been reported for patients aged 15–20 years treated in paediatric departments compared with those of a similar age treated by community internists [20, 21]. In addition, the parents of children with cancer are usually more compliant with intensive, prolonged chemotherapeutic regimens than adult patients are.

3. Outcome of AYA-ALL on different protocols

Significant progress has been made in the treatment of ALL in both paediatric and adult patients over the past 40 years (Table 2) [12,22–24]. However, whereas around 80% of children 1–10 years old are long-term survivors with current therapies, only 30–40% of adult patients are cured. Adolescents and young adults have an intermediate outcome. Numerous paediatric studies have confirmed that adolescents have a worse prognosis than

[1] Editor's footnote: This is an important point, but it is not yet known when, age-wise, decreasing drug tolerance becomes a critical 'risk factor'. It seems unlikely that teenagers' tolerance is really less than that of younger children. Perhaps compliance is the real issue (J.P.).

Table 2
Approximate ALL cure rates (%) by time period

Era	Paediatric	Adult
1960s	30–40	<5
1970s	40–50	10
1980s	50–70	20–30
1990s	65–80	30–40

Refs. [12,22–24].

children 1–9 years of age, despite more intensive therapies [2,25–27]. In 1993, the United States Cancer Therapy Evaluation Program (CTEP) and National Cancer Institute (NCI) sponsored a workshop that included representatives from the Children's Cancer Group (CCG), Pediatric Oncology Group (POG), Dana-Farber Cancer Institute and St. Jude Children's Research Hospital [28]. Uniform criteria for risk-based treatment assignment in children with ALL were recommended. Standard-risk ALL, associated with a 4-year event-free survival (EFS) of 80% was clinically defined by age at diagnosis of between 1 and 9 years and a total leucocyte count of $<50\times10^9$/l at diagnosis. Patients with other presentations were considered to be at high risk of relapse with a 4-year EFS of only 65%. It was agreed that the 'risk groups' may be refined by diagnostic factors other than age and leucocyte count, such as the specific biological properties of leukaemic cells and early response to treatment.

In adult studies, those younger than 35 years achieve complete remission more frequently and have a better remission duration and survival than older patients [3,4,13]. The Memorial Sloan-Kettering Cancer Center (MSKCC) reported worse remission rates, shorter remission duration, and inferior survival in adults (>15 years) compared with children <15 years treated on a similar intensive regimen (L-2) [29]. In recent studies, including the latest MSKCC protocols, adolescents have been treated either on paediatric or adult trials. Meaningful comparison of outcomes is difficult because of variation between study groups and patient populations. Still, older patients consistently have a poorer outcome in both paediatric and adult trials.

Lately, the outcome of AYA-ALL managed with either paediatric or adult cooperative group protocols has been compared in two reports. The outcome of 196 patients of 16–21-year-olds treated on the paediatric CCG protocols was compared with that of 103 patients of the same age group treated on the adult Cancer and Leukemic Group B (CALGB) protocols between 1988 and 1998. The complete remission (CR) rate and 6-year EFS were 96 and 64% with the CCG regimens compared with 93 and 38% with the CALGB protocols [30]. In another report, 77 patients ranging from 15 to 20 years at diagnosis treated on the paediatric FRALLE-93 between 1993 and 2000 were compared with 100 patients of the same age group who received the adult LALA-94 schedule. The CR rate was 94% on French Acute Lymphoblastic Leukemia Group (FRALLE), with a 5-year EFS of 67% compared with 83% CR and 41% EFS on the French Group for Treatment of Adult Acute Lymphoblastic leukemia (LALA) protocol [31]. Although the median age of patients treated on the adult schedules was rather higher, it does not explain alone the significant difference in outcome for this group with a narrow age range.

At the M.D. Anderson Cancer Center, 204 patients (16–79 years) treated on a schedule known as 'Hyper-CVAD' achieved a 91% CR rate and 39% 5-year EFS. Patients <30 years at diagnosis in this group had a 98% CR rate and 54% 5-year EFS [3]. These results are significantly superior to the adult cooperative group outcome which could reflect (a) the use of a more effective treatment regimen, (b) greater expertise in a single, large cancer centre with a well-developed leukaemia programme, or (c) both.

4. Lessons learned

Although the outcome for AYA with ALL is intermediate between that of younger children and older adults in all published studies, available data indicate that patients in this age group fare better on paediatric protocols. These observations were made using a retrospective analysis of relatively heterogeneous populations, with different therapies, little data on actual drug dosages delivered, and different treatment delivery settings. As a consequence, it is difficult to draw meaningful specific conclusions. ALL outcome depends on a number of variables related to disease biology, host factors, pharmacokinetics and treatment. Different regimens must be studied not only for their influence on outcome, but also for other variables that could influence response. For example, the L-10 regimen resulted in different outcomes when used at MSKCC [32], Southwest Oncology Group (SWOG) [33], or the University of Iowa [34], illustrating the difficulty inherent in comparisons of clinical trial results between different centres. To make progress in curing ALL in the AYA age group, paediatric and adult oncologists have to bridge the current gap and work together more effectively to establish the most effective, least toxic regimen for these patients.

5. Future directions

In adolescents and young adults with ALL, disease biology, tolerance to therapy and outcome are similar. At present, the relatively small numbers of 'AYA' with ALL are treated, according to loose referral patterns, either with adult or paediatric protocols. Over the past two

decades, immunophenotyping, cytogenetics and molecular genetics have helped design therapies that target leukaemia subtypes. The latest advances in molecular genetics and proteomics should promote the use of more selective, 'targeted' therapies in an effort to improve outcome and reduce toxicities. Further improvement in ALL outcome is likely to evolve from therapies tailored to disease biology rather than age. Paediatric and adult oncologists in national cooperative groups and at major cancer centres should follow unified protocols for adolescents and young adults with ALL. These patients should be referred to research treatment centres with experience in the management of ALL, and should be enrolled on studies. They should also benefit from international collaboration that has been successful in other rare paediatric tumour types such as Wilms' tumour and neuroblastoma. Using this kind of approach, it should be possible to establish more effective regimens, and to determine the role that differences in practice and compliance between paediatricians and internists play in AYA-ALL outcome.

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