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The adolescent and young adult with cancer: State of the art--acute leukemias

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Abstract

Despite survival gains over the past several decades, adolescent and young adult (AYA) patients with both acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) demonstrate a consistent survival disadvantage. The AYA population exhibits unique disease and host characteristics, and further study is needed to improve their outcomes. This review will highlight distinctive aspects of disease biology in this population, as well as salient treatment-related toxicities including osteonecrosis, pancreatitis, thromboembolism, hyperglycemia, and infections. The impact of obesity and differences in drug metabolism and chemotherapy resistance will also be discussed, as well as optimal treatment considerations for the AYA population.

Keywords

Acute lymphoblastic leukemia; acute myeloid leukemia; adolescent; young adult; treatment-related toxicity; osteonecrosis; pancreatitis; thromboembolism; hyperglycemia; obesity; adherence

Introduction

Due to unique features of both host and disease biology, there has been increasing recognition of the adolescent and young adult (AYA) population as a distinct patient subgroup within the acute leukemias. This patient group, defined by an age range of approximately 15–35 years, deserves special attention as a group with unique disease and host characteristics and psychosocial needs, lying at the intersection of adult and pediatric oncology, but not fitting altogether neatly into either area. Continued study of the AYA population is critical, as outcomes remain markedly inferior to those of younger patients, despite improvements over time. In a recent review of outcomes in childhood acute lymphoblastic leukemia (ALL) on Children's Oncology Group (COG) protocols, even for children treated in the most recent era between 2000–2005, outcomes decreased significantly with increasing age. The 5-year overall survival was $94.1 \pm 0.4\%$ for patients 1–9.99 years; $84.7 \pm 1.5\%$ for patients 10–14.99 years; and $75.9 \pm 2.6\%$ for patients 15–21.99 years[1]. Survival decreases progressively with increasing age in most acute myeloid leukemia (AML) subtypes as well, according to an analysis of 17 SEER cancer registries

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Compliance with Ethics Guidelines

Conflict of Interest

M. Monica Gramatges declares no potential conflict of interest.

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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

containing data for patients diagnosed from 2001–2006 [2]. This review will highlight some of the key differences in disease biology and treatment-related toxicities, and conclude with a discussion of optimal treatment considerations for the AYA population.

Disease biology in AYA patients with leukemia

The classic cytogenetic lesions of ALL differ markedly in prevalence in adult and pediatric populations. Favorable lesions (e.g., the *ETV6-RUNX1* fusion and high hyperdiploidy) are more frequent in childhood B-lineage ALL, whereas unfavorable lesions (e.g., *BCR-ABL1* fusion, *MLL* rearrangement, and hypodiploidy) are more frequent in adult ALL. Several novel genetic alterations have been recently identified which are also associated with an adverse prognosis, and these unfavorable lesions are also more frequent in adolescent and adult ALL patients; these include *JAK* mutations, *CRLF2* rearrangements, *IKZF1* deletions and mutations, intrachromosomal amplification of chromosome 21 (iAMP21), and the Philadelphia-chromosome-like gene expression signature [3]. Combined data from the trials ALL-BFM 86 and ALL-BFM 90 demonstrate that several other adverse prognostic features also occur more frequently in older patients: high initial white blood count, CNS involvement, and a prednisone poor response [4].

T-lineage ALL occurs more frequently in older patients (comprising 10–15 % of pediatric and 25 % of adult ALL), and is characterized by a variety of chromosomal translocations. Gene expression profiling studies indicate that TALL cases form four main subgroups, characterized by rearrangements that involve *TAL/LMO*, *TLX3/HOX11L2*, *TLX1/HOX11*, and *HOXA* [5]. Differences in the relative frequencies of each subgroup in pediatric and adult T-ALL may reflect age-related changes in the thymic population of cells at risk for malignant transformation [6]. Unlike for B-lineage ALL, age does not have a strong inverse correlation with survival in T-lineage ALL [7]. The recently identified early T-precursor subtype of T-ALL appears to have a similar incidence of approximately 10 %, and similarly unfavorable prognosis in both adult and pediatric T-ALL [8].

In AML, there has been a recent surge in identification of gene mutations present in cases with normal karyotype [9, 10]. *FLT3-ITD* mutations are associated with a poor prognosis in all age groups, and increase in frequency with age. *NPM1* mutations are associated with more favorable prognosis, and also occur more often in adult AML. *N-RAS* and *CEBPA* mutations occur with similar frequency across pediatric and adult age groups. *IDH1*, *TET2*, *NPM1*, and *DNMT3A* mutations occur less often in younger patients. Interestingly, the prognostic importance of mutations is not always the same in adult and pediatric age groups; for example, *KIT* mutations have been found to have adverse prognostic significance in adult but not pediatric AML [11].

Treatment-related toxicities in AYA patients with leukemia

As therapies for both ALL and AML have intensified, toxicities related to treatment have increased substantially. Experiences with treating leukemia in the AYA population indicate that these toxicities increase in both number and severity with advancing age. Age-specific differences related to pubertal changes, body mass index, and drug metabolism and sensitivity may contribute to the higher incidence of treatment-related toxicities in AYA leukemia.

Steroid-related osteonecrosis

Osteonecrosis, or avascular necrosis (AVN), results from a temporary or permanent loss of blood supply to the bone resulting in the destruction of articular surfaces within a joint, most commonly affecting the hips, knees, shoulders, and ankles. Development of AVN is

associated with exposure to corticosteroids, an integral agent to combat childhood ALL. AVN symptoms include arthritic pain and decreased range of motion, often localized to weight-bearing joints such as the hips and knees. Treatment for this condition, depending on the severity of presentation, may include steroid discontinuation, physical therapy, and/or total joint replacement.

Dexamethasone is 5–6 times more cytotoxic in ALL cell lines than prednisone [12], findings that have translated to a significantly improved event free survival in standard risk ALL patients randomized to dexamethasone in the Children's Cancer Group (CCG) protocol 1922 [13], MRC ALL97/99 [14], and in BFM-2000 [15]. In addition to better cytotoxicity, these results are attributed to dexamethasone's longer half-life and more effective CNS penetration than prednisone, therefore reducing the likelihood of CNS relapse [16, 17, 13]. Trials within the CCG, the Dana Farber Cancer Institute (DFCI), and the COG utilizing dexamethasone have demonstrated a higher than expected incidence of AVN [18–21], although a meta-analysis of six trials that randomized dexamethasone and prednisone in pediatric ALL therapy failed to demonstrate a significant difference in incidence of AVN related to type of steroid used [22].

The AYA population is significantly more susceptible to AVN than younger children. In CCG 1882, AVN occurred in 14.2 % of participants aged 10–20 years, compared with 1 % of children aged 1–9 years [18]. CCG 1961 described similar findings, with the older AYA population (age greater than or equal to 16 years) demonstrating particularly high risk for AVN with a remarkably high incidence of 19.9 % [23]. The pediatric AIEOP-ALL 95 trial noted an overall incidence of symptomatic AVN of only 1.1 %; however, again the incidence was significantly higher in subjects aged 10 to 17 years (7.4 %, $p < 0.0001$) [24]. Similar findings were noted in the St. Jude Total Therapy XV study, with grade 3 or 4 AVN significantly more common in the 15–18 year old group compared with the 1–14 year old group [25]. In addition to age over 10 years, additional risk factors for AVN in ALL include female gender, white race, high BMI, as well as various genetic factors [26–31].

The risk of AVN is significantly reduced with the use of discontinuous dosing of dexamethasone, e.g., during delayed intensification [32]. Treatment recommendations for symptomatic patients include a low threshold for use of MRI imaging as a means for diagnosis, early physical therapy, and consideration of use of bisphosphonates in conjunction with steroid discontinuation [33]. In order to mitigate the side effect of AVN, COG has adopted the use of prednisone during Induction chemotherapy in children greater than 10 years old, in addition to discontinuous dexamethasone during delayed intensification [34]. A prospective study of the incidence and natural history of AVN is ongoing for a subset of patients enrolled on the current COG high-risk ALL treatment study.

Asparaginase-related pancreatitis and thromboembolism

The incidence of asparaginase-associated pancreatitis in childhood ALL ranges from 5 to 18 %, but AYA patients are at significantly increased risk [35, 36]. Using a regimen comprised of intensive asparaginase for 30 weeks, the DFCI noted markedly high rates of asparaginase-related toxicities in the 9–18 years age group compared with younger children (48 % vs. 24 %). The incidence of pancreatitis in the older age group was 15 % compared with 5 % in younger children [37]. Thromboembolism, also associated with asparaginase, was also more likely to occur in children greater than 10 years old (44 %) than in younger children (4 %) treated on DFCI ALL protocols, although this effect may also have been related to steroid dosing in high-risk patients [38]. Other groups using less intensive asparaginase dosing have also observed increased drug-related toxicity in the AYA population. The St. Jude Total Therapy XV study noted grade 2 or higher thromboembolism to be significantly more common in the 15–18 year old group compared with the 1–14 year old group [25]. In CCG

1961, patients aged 10 years and older were significantly more likely to suffer stroke than those under the age of 10 years [23]. In AYA patients, who are at substantially higher risk for asparaginase-related adverse events than younger children, obtaining a baseline pancreatic lipase prior to asparaginase administration, combined with early attention to symptoms of anorexia or abdominal pain, is recommended. Delaying placement of a central line until after the induction phase of treatment may help minimize thrombotic risk.

Steroid and asparaginase-related hyperglycemia

Hyperglycemia is a common side effect of ALL therapy, occurring in 10–15 % of pediatric patients [39, 40]. Elevated blood glucose is typically noted within one week of the first dose of asparaginase in the context of daily steroids, with the primary risk factors being older age, obesity, and family history [40]. Increased risk for hyperglycemia in the AYA population is likely a consequence of post-pubertal changes in estrogen and testosterone, and has been associated with increased risk for infection, particularly bacteremia/fungemia and cellulitis [41]. In CCG 1961, patients over 16 years of age were more likely to develop hyperglycemia than patients aged 1–9 years, or even than patients aged 10–15 years [23]. A series of four St. Jude Total Therapy studies showed age greater than 10 years as the only factor associated with hyperglycemia after multivariate analysis, though in this study, no difference in infection risk was noted [39]. Further evaluation of the consequences of hyperglycemia found that older patients were also at higher risk for developing diabetic ketoacidosis [42]. Similarly, the St. Jude Total Therapy XV study demonstrated a higher incidence of grade 3 or 4 hyperglycemia in adolescents than in children 14 years old and younger [25]. Given the high risk for hyperglycemia in the AYA population, further research is needed to determine the optimal timing for measuring fasting blood glucoses during induction therapy in these individuals, so that early intervention can prevent consequent morbidities.

Obesity

Older age is also a risk factor for obesity, which has been independently associated with poor outcomes in both ALL and AML. In a series of CCG ALL studies, older patients were more likely to be obese, with a 68 % 3 year OS in obese subjects compared with 80 % in the nonobese. In these studies, obesity proved to be one of the principal determinants of relapse; however, obesity had no effect on the incidence of toxic deaths [43]. In contrast, a large retrospective review in children with ALL showed no association between body mass index (BMI) and outcomes [44].

With regards to AML, in CCG-2961, morbidly obese individuals were significantly more likely to be both older and present with higher white blood cell counts than non-obese subjects. Morbid obesity was associated with reduced EFS and OS, including a higher incidence of treatment-related mortality [45]. Interestingly, parameters for measuring chemotherapeutic effect, such as time to count recovery, did not support over-dosing as a reason for excess treatment-related toxicities. Rationale for poor outcomes in obese patients may be due to differences in drug distribution volume, particularly with regard to solubility of the agent in water vs. lipid [46]. Various single agents have been studied in small numbers of patients relative to their clearance in obese individuals. One pharmacokinetic study has suggested that the observed increased risk for relapse in the obese may in part be due to under-dosing of mercaptopurine, used in ALL maintenance therapy, as a result of calculations based on body surface area [47]. Therefore, at least in cases of ALL, the higher risk for relapse associated with obesity may be due to metabolic differences during maintenance therapy after remission is achieved. Current available evidence seems to suggest that initial dosing should be made based upon actual body weight, adjusted as needed over time for changes in BMI, and as recommended by the treatment protocol based upon target neutrophil counts. Additional pharmacokinetic studies are needed to better

understand the influence of drug metabolism and BMI upon treatment outcomes. With regards to long-term effects of ALL therapy, though all patients including AYAs are at risk for obesity, those at the highest risk for developing post-treatment obesity are younger children, particularly females, treated with CNS radiation [46]. The obesity epidemic has become increasingly common, disproportionately affecting the AYA population. Long-term follow up studies, such as those undertaken by the Childhood Cancer Survivor Study, are critical to determining risks for obesity in survivors of this age group, so that adequate means of prevention and education may be implemented.

Drug metabolism and resistance

Age dependent factors in drug metabolism are also likely to play a role in treatment-related toxicities for both ALL and AML. For example, increasing age and longer exposure to elevated plasma methotrexate concentrations have been associated with a significant risk for elevated liver enzymes in ALL patients receiving high-dose methotrexate infusions [48]. In addition, children under the age of 10 years exhibit a methotrexate clearance that is twice as fast as the clearance observed in children older than 10 years [49, 50]. As noted above, many drugs commonly used in the treatment of childhood leukemias are associated with an adverse effect profile that is age dependent. Changes in drug distribution occurring with growth and development, delayed maturation of drug metabolizing enzymes, age-dependent changes in renal and hepatic function, and hormonal changes together account for significant differences in drug metabolism in children compared with adults, potentially affecting therapeutic response and tolerance [51, 52].

The in vitro sensitivity of leukemic blasts isolated from children and adults with ALL has been extensively examined, with results suggesting that leukemia cancer biology may also be age-dependent. Fourteen drugs used in ALL therapy were examined for evidence of ALL cellular drug resistance using the MTT assay, with higher IC₅₀ values for all 14 agents in adult ALL samples compared with pediatric samples. These results were statistically significant for cytarabine, asparaginase, daunorubicin, dexamethasone, and prednisone, all mainstays of high risk ALL therapy [53]. Therefore, aside from inherent age-related factors contributing to increased toxicities, failure to fully eradicate the leukemic clone due to chemoresistance may also play a role in the increased risk for relapse observed in older individuals. Relative glucocorticoid resistance in adults compared with children diagnosed with ALL has also been demonstrated [54].

Treatment-related mortality and infection risk

Historically, older age within the AYA population independently predicted poor prognosis in treatment for ALL, with 5 year OS falling from 61.4 % in patients aged 15 to 20 years to 44.8 % in young adults aged 20–30 years [55]. However, with contemporary therapies administered in pediatric centers, EFS and OS for the AYA subgroup has improved substantially, and has grown increasingly similar amongst all patients over the age of 10 years [56, 23, 57, 25]. Nonetheless, treatment-related mortality in the AYA population remains considerably higher than what is observed in younger age groups. This may in part be due to an increase in early treatment-related deaths. For example, age greater than 10 years is an independent risk factor for tumor lysis syndrome during ALL induction [58]. In CCG 1961, AYAs aged 16–21 years were more likely to experience death after induction failure, relapse, or second cancer compared with younger patients (80.3 % of patients experiencing one of these events, vs. 68.5 % of children aged 10–15 years and 60 % of patients aged 1–9 years) [23]. In the St. Jude Total Therapy XV study, no significant difference in EFS or OS was noted between adolescents and younger children, with outcomes in adolescents markedly improved compared with prior studies. However, a higher incidence of toxic deaths in this older group did occur, primarily due to infection [25]. For

the previous five St. Jude Total Therapy studies, the cumulative incidence of death in pediatric ALL was higher in both infants under the age of one year and in children greater than 10 years (5.8 % in patients age > 10 years vs. 1.6 % in patients age 1–9 years) [59]. A recent review of two DFCI ALL protocols indicated no significant difference in EFS in relation to age, but 5 year OS differed substantially, decreasing from 92 % in children aged 1–10 years, to 78–81 % for those aged 10–15 years and 15–18 years [56]. In this series, no difference in treatment-related mortality between age groups was observed.

This is an even more relevant concern in pediatric AML, where overall treatment-related mortality in larger trials has ranged from 11–14 % [60, 59, 61]. Age greater than 10 years at diagnosis was associated with cumulative incidence of death in a review of four St. Jude AML studies, AML-83, AML-87, AML-91, and AML-97 (12.4 % in patients age > 10 years vs. 2.3 % in patients ages 1–9 years) [59]. A combined review of patients diagnosed at both MD Anderson Cancer Center (MDACC) and St. Jude showed age to be a risk factor for AML treatment-related adverse events in the recent era of increased treatment intensity (4.3 % increase in number of relapse or death events per year of age for patients greater than 10 years, an effect not observed in younger subjects) [62]. In addition, the BFM group showed an increase in treatment-related deaths after day 15 of AML therapy to be significantly associated with age greater than 10 years, with fatal infections as the primary cause of death [63].

Higher incidence of infections has been documented in AYA patients with both ALL and AML. In the St. Jude Total Therapy XV study, grade 4 or 5 infections were significantly more common in children with ALL ages 15–18 years than in those under the age of 15 [25]. In the AML CCG-1961 study, children older than 16 years were more likely to experience microbiologically documented infections [64]. CCG-2891 confirmed these findings, showing children older than 10 years to have higher rates of fungal infection following intensive consolidation or transplantation [65]. Together, these results encourage careful vigilance for fever in the setting of neutropenia, and potential benefit to antibiotic and antifungal prophylaxis during ALL and AML induction therapy for the high-risk AYA population, as recommended, albeit based upon limited pediatric data, by the Infectious Disease Society of America [66, 67].

Optimal treatment regimens

In ALL, numerous studies have demonstrated a survival advantage for AYA patients treated on pediatric versus adult treatment regimens [68, 69]. This may be due to a variety of factors including higher cumulative doses of nonmyelosuppressive chemotherapy agents such as vincristine, glucocorticoids, and asparaginase, for which historically there has been concern for increased toxicity in adults; lower likelihood of dose reductions and delays by pediatric vs. adult oncologists; and higher likelihood that AYA patients treated at pediatric centers have a strong family and social support system. A large prospective study (C-10403) is currently in progress to evaluate outcomes for AYA patients with ALL who are treated on a standard pediatric-based treatment regimen.

In AML, pediatric regimens tend to be comprised of several courses of multi-agent chemotherapy, whereas adult regimens generally treat with single-agent cytarabine after the first induction cycle. Hematopoietic stem cell transplantation is offered to a higher proportion of adult AML patients. There are many fewer retrospective studies in AML comparing outcomes for AYA patients treated on pediatric versus adult protocols, and the results are mixed, with some showing a benefit to pediatric protocols and others showing no difference [69].

In ALL, where prolonged oral chemotherapy constitutes the backbone of the essential maintenance phase of therapy, treatment adherence is another factor that is crucial to outcome, and poses a particular challenge in the AYA population. Bhatia et al. found that 59 % of all ALL relapses were attributable to nonadherence[70], and that age over 12 years was associated with significantly lower mercaptopurine treatment adherence during ALL maintenance therapy (85.8 % vs. 93.1 %, $p < 0.001$). Potential approaches to improving adherence in the AYA population include attention to communication style, psychosocial support, minimizing impact upon lifestyle and peer activities, and use of rewards and reinforcements[71].

Conclusion

As outcomes improve in the treatment of acute leukemias, specific strategies will be necessary to address the persistence of adverse outcomes in particularly high-risk subgroups. In the past, the AYA population has not received consistently adequate attention from either adult or pediatric oncologists; however, there is a growing recognition of the distinct biologic features and toxicity profile of this group. We are now poised to build on these insights by developing novel therapeutic approaches that target specific genetic alterations, reducing treatment-related toxicities through both prevention and optimal supportive care, and implementing treatment regimens that maximize treatment intensity and adherence.

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