Malignant hematologic diseases in adolescents and young adults

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Adolescents and young adults (AYA) with cancer have been designated as a vulnerable population by the National Cancer Institute. This group, defined by the ages of 16-39 years, has not enjoyed the same survival improvements over the past several decades as older and younger cohorts. Several barriers prevent the optimal delivery of oncologic care in this subpopulation. This review will describe these challenges in the context of the major hematologic malignancies affecting this population (acute lymphoblastic leukemia [ALL], acute myeloid leukemia [AML], Hodgkin lymphoma [HL], and non-Hodgkin lymphoma [NHL]). For example, historical differences in care delivery between pediatric and adult health care systems have created confusion about optimal treatment planning for AYAs, a population that spans the pediatric-adult divide. In the case of ALL, retrospective studies have demonstrated significantly better outcomes when AYAs are treated according to pediatric and not adult protocols. Additional challenges more specific to AYAs include increased treatment-related toxicity relative to younger patients; less access to care and, specifically, access to clinical trials; lower adherence to medications and treatment plans; and psychosocial stressors relevant to individuals at this stage of life. Recognizing and responding to these challenges in AYAs may create opportunities to improve the cancer outcomes of this group. (Blood. 2011;117(22):5803-5815)

Introduction

Adolescents and young adults (AYA) with cancer are considered a “high-risk” group. Epidemiologic studies based on US Surveillance, Epidemiology, and End Result (SEER) data show that survival improvements for all cancers among AYAs (defined as 16- to 39-year-olds) have lagged behind younger and older cohorts.¹ The prognosis for younger individuals with acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) is superior to the prognosis for AYAs, and the prognosis for older individuals with other malignancies, such as breast cancer, may be better than that for AYAs.² AYAs with cancer are also considered “high risk” because of unique sociological challenges in this population, including delays in diagnosis, insurance barriers,³ low rates of clinical trial enrollment,⁴ problems with adherence to medications and care plans,⁵ and psychosocial considerations including growing independence, young children at home, and supportive care needs.⁶ Recognizing this, in 2006 the National Cancer Institute convened an Adolescent and Young Adult Oncology Program Review Group (AYAO PRG).⁷ More recently, the American Society of Clinical Oncology and LIVESTRONG launched an initiative called “Focus Under Forty,” an educational curriculum for physicians to raise awareness about these issues (www.university.asco.org/focusunder40).

Hematologic malignancies in AYAs

A recent period analysis of survival among AYAs with hematologic malignancies in the United States presents a mixed picture of success.⁸ Although 10-year relative survival estimates have increased for all diseases between 1981-1985 and 2001-2005, survival rates among AYAs with hematologic malignancies have not matched the levels achieved by children, with the exception of Hodgkin lymphoma. Additionally, survival rates for AYAs with AML and ALL appear to have essentially plateaued in the 1990s. In contrast, outcomes for children younger than 15 years of age with these diagnoses appear to have continued to exhibit slow and steady improvement throughout the most recent periods of examination.⁹,¹⁰ Geographic variations in AYA survival rates in a European study suggest that nonbiologic factors related to care delivery may have an important impact on outcome.¹¹

Organization of pediatric and adult health care delivery

In the United States and around the world, pediatric and adult health care systems have evolved separately. Dedicated children’s hospitals in many urban areas provide inpatient and outpatient services that are not geographically proximate to services provided for adults. Separate training programs and subspecialty societies have emerged within adult and pediatric medicine. Typically, the transition between pediatric and adult health care occurs around the age of 18 years, mostly for historical rather than biologic reasons. This separation has created challenges for AYAs, in part because most of the attention within each of these specialties naturally focuses on the “average” patient near the median of the respective age distributions, rather than at the margins, where AYAs reside. This can lead to confusion regarding optimal treatment approaches for AYAs.

For some diseases, AYAs with “pediatric-like” cancers fare better when treated by pediatric oncologists, and those with “adult-like” malignancies have better outcomes with adult oncologists.¹² In pediatric oncology, standards of care for specific
malignancies are essentially defined by ongoing clinical trials. Although specific protocols may differ worldwide, the clear majority of younger patients with cancer are treated at pediatric institutions on studies. Sequential studies evolve from one another in an iterative manner. In contrast, most adults are treated off studies in community settings. Thus, standards of care in adult oncology are based on previous studies, published guidelines, or historical experience, rather than explicitly defined by ongoing studies.

Many pediatric protocols have upper age limits exclusive of the majority of the AYA population, and many AYAs receive care off trial in adult health care settings. It is not clear whether AYAs would benefit more from pediatric-like treatment approaches, inspired by protocols designed to maximize treatment intensity while minimizing long-term and late effects, or from adult standards of care, typically designed for a population with a median age that is significantly higher. The following sections will review pediatric and adult treatment patterns and implications for AYAs within the major hematologic malignancies.

### Ph-negative ALL

#### Incidence

Using US SEER data, annual rates for new diagnoses of ALL in the United States vary from 2.1-7.7/100 000 in children up to age 15, 0.6-1.7/100 000 in AYAs, and 0.6-1.8/100 000 in adults over the age of 40.

#### Pediatric

Pediatric approaches for the treatment of Ph-negative (Ph⁻) ALL originated in the late 1960s and early 1970s, with the development of the original Berlin-Frankfurt-Münster (BFM) backbone. This treatment incorporated multidrug induction chemotherapy, early risk stratification, delayed intensification, central nervous system (CNS) prophylaxis, and prolonged maintenance therapy. Carefully planned sequential trials within pediatric cooperative groups and institutions around the world demonstrated that continuous improvement can be achieved through study, modification, addition, or subtraction of individual components of therapy as well as methodical ongoing enhancements of supportive care. Recently, 77 studies from 15 study groups were re-analyzed to update long-term outcomes for 52,891 pediatric patients treated between 1980 and 2007. Together, these data showed cure rates of at least 80% by the end of the 1990s, and it is estimated that 85%-90% of children diagnosed with Ph⁻ ALL today will be cured. Recent findings from controlled pediatric studies that have led to further improvements include the recognition of the prognostic importance of minimal residual disease (MRD) and its use in subsequent treatment stratification; the value of stronger early intensification for higher-risk patients; the suggestion that cranial irradiation can be safely omitted from standard therapy; and the role of dexamethasone as a replacement for prednisone as part of initial treatment.

#### Adult

Because of the high success rates achieved in pediatric Ph⁻ ALL, adult protocols emulated certain pediatric features. Most regimens included vincristine, a corticosteroid, and an anthracycline, with subsequent cycles including various combinations of agents and doses. More variation existed across adult regimens than pediatric regimens, and the timing and doses of the individual components from induction through consolidation, intensification, and maintenance in the adult regimens were usually not subjected to the same type of scrutiny through sequential trial design as was the case in pediatric trials. The Cancer and Leukemia Group B (CALGB) ALL regimen used a 5-drug combination modified from regimens used in high-risk pediatric ALL, given in 5 courses of treatment across 24 months. The Group for Research on Adult Acute Lymphoblastic Leukemia (GRAALL) 2003 regimen used similar agents in remission induction, with distinctions for good early responders and poor early responders, and then included agents in subsequent cycles with different timing, routes, and dosages than in the CALGB protocol. The HyperCVAD regimen, developed and refined at M. D. Anderson Cancer Center (MDACC), omitted asparaginase and used cycles of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and high-dose cytarabine. This regimen also included CNS prophylaxis with intrathecal methotrexate and intrathecal cytarabine. In general, the adult protocols achieved encouraging complete response rates to induction therapy (up to 80%-90%), although longer-term disease-free survival (DFS) and overall survival (OS) rates have remained in the 30%-50% range for many years.

#### AYAs

In the early 2000s, several retrospective studies compared the outcomes of AYAs treated on pediatric or adult protocols for Ph⁻ ALL, and found markedly different results (Table 1). In France, 15- to 20-year-olds treated on the pediatric FRALLE-93 trial had a higher 5-year event-free survival (EFS; 67%) than those treated on the adult LALA-94 (41%, P < .0001). Similar differences were observed in other countries including the United Kingdom, Italy, the Netherlands, Sweden, Finland, and the United States, where adolescents on the pediatric Children’s Cancer Group (CCG) study had a 7-year EFS of 63% compared with a 7-year EFS of 34% for those treated on the adult CALGB trial (P < .001). Explanations for these findings included differences between the protocols (examples provided in Table 2), with the pediatric studies including higher doses of the nonmyelosuppressive agents (corticosteroids, vincristine, asparaginase), earlier and

### Table 1. Retrospective data for AYAs treated on representative pediatric or adult ALL protocols

<table>
<thead>
<tr>
<th>Trial</th>
<th>Pediatric</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRALLE-93/LALA-94</td>
<td>5-y EFS: 67%</td>
<td>5-y EFS: 41%</td>
</tr>
<tr>
<td>CALGB/CCG</td>
<td>7-y EFS: 63%</td>
<td>7-y EFS: 34%</td>
</tr>
<tr>
<td>MRC ALL 97-99/UKALLXII-E2993</td>
<td>5-y EFS: 65%</td>
<td>5-y EFS: 49%</td>
</tr>
<tr>
<td>GIMEMA/AIEOP</td>
<td>2-y OS: 80%</td>
<td>2-y OS: 71%</td>
</tr>
<tr>
<td>HOVON/OCOG</td>
<td>5-y EFS: 71%</td>
<td>5-y EFS: 38%</td>
</tr>
<tr>
<td>Adult ALL Grp/NOPHO-92</td>
<td>5-y OS: 74%</td>
<td>5-y OS: 39%</td>
</tr>
<tr>
<td>Finnish Leukemia/NOPHO</td>
<td>5-y OS: 67%</td>
<td>5-y OS: 60%</td>
</tr>
</tbody>
</table>

EFS indicates event-free survival; and OS, overall survival.

### Table 2. Examples of historical differences between adult and pediatric ALL protocols

<table>
<thead>
<tr>
<th>Component</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-myelosuppressive drugs (glucocorticoids, vincristine, L-asparaginase)</td>
<td>Greater amounts in pediatric protocols</td>
</tr>
<tr>
<td>CNS prophylaxis</td>
<td>Earlier and with greater frequency in pediatric protocols</td>
</tr>
<tr>
<td>Long-term maintenance therapy</td>
<td>Longer duration in pediatric protocols</td>
</tr>
</tbody>
</table>

CNS indicates central nervous system.
more intensive CNS therapy, greater use of MRD to guide risk stratification, somewhat different timing and type of postremission therapy, and sometimes longer duration of maintenance treatment. Recent results from AYAs treated on pediatric-like protocols have been promising. In Spain, 6-year EFS and OS for 18- to 30-year-olds using this approach are 61% and 69%, respectively.36 The Dana-Farber Cancer Institute has successfully treated adolescents with an intensive, pediatric-like protocol (78% 5-year EFS in 15- to 18-year-olds) and has expanded this approach to adults up to the age of 50.37 Representative data presented at the American Society of Hematology annual meeting in 2010 showed a 5-year EFS of 57% and 5-year OS of 67% for AYAs (15- to 29-year-olds) in France treated on pediatric protocols38; data from M. D. Anderson showed 2-year OS and DFS of 91% and 85%, respectively, for patients up to the age of 25 years, and 2-year OS and DFS of 55% and 61%, respectively, for patients aged 25-40 years treated with pediatric-like BFM therapy.39 The large US pediatric and adult cooperative groups have collaboratively devised and are conducting a phase 2 study that enrolls AYAs up to the age of 39 on a standard pediatric ALL regimen (approach summarized in Table 3). Thus, in AYAs with Ph⁻ ALL, it seems (so far) that outcomes can be improved by using pediatric protocols. Mature trial data are awaited to confirm this hypothesis.

Recommendations

There are no prospective studies that demonstrate that an adult-like or pediatric-like therapeutic approach is superior for AYAs with Philadelphia chromosome-negative ALL. However, multiple retrospective studies suggest that a pediatric-like approach may be superior in this patient population, and several cohort studies are beginning to demonstrate the feasibility of this approach. In general, because of the complexity of ALL treatment protocols and the importance of adherence to therapy, we recommend that AYAs with Ph⁻ ALL are treated in centers with significant experience in this disease. We also recommend that, if possible, AYAs with Ph⁻ ALL are enrolled onto prospective studies investigating pediatric-like approaches. Important unresolved issues needing study in the future include the role of stem cell transplantation in AYAs with Ph⁻ ALL who are in remission following pediatric-like therapy, and the preferred treatment approach for AYAs with Ph⁺ ALL.

Acute myeloid leukemia

Incidence

Using US SEER data, annual rates for new diagnoses of AML in the United States vary from 0.4-1.5/100 000 in children up to age 15, 0.9-1.3/100 000 in AYAs, and 1.6-23.2/100 000 in adults over the age of 40.

Pediatric

Pediatric AML trials in large institutions and cooperative groups have evolved sequentially in a manner similar to pediatric ALL trials. Although outcomes with AML have been worse, results have improved with time, with increasing success rates largely attributed to intensification of therapy and improvements in supportive care.40 Contemporary pediatric approaches (Table 2) often include 2 planned courses of induction chemotherapy, such as intensively timed IdaDCTER as used in CCG-2961,41 or the current Children’s
Oncology Group (COG) strategy (as in AAML0531) involving a later course of second induction timed by MRD-based risk. Postremission therapy typically includes at least 2 additional courses of intensive multi-agent treatment involving high-dose cytarabine. CNS prophylaxis is often used, although there is debate about its efficacy. Transplantation is typically reserved only for high-risk patients. In the CCG-2961 study, improvements in supportive care throughout the trial reduced treatment-related mortality from 18% at the beginning to 9% by the end. Complete remission, 5-year OS, and 5-year EFS for patients under the age of 21 were 88%, 52%, and 42%, respectively, with similar results internationally (including 5-year OS estimates 60% in several cases). More recently, in the Japanese AML 99 trial, patients under the age of 18 were risk-stratified to receive either one or two 2-week multi-agent induction courses and triple intrathecal therapy, followed by 5 or 6 consolidative courses using an etoposide and cytarabine backbone in addition to other agents. Reported results include a 5-year OS of 76% and 5-year EFS of 62%. At St Jude’s and collaborative institutions, 232 patients up to the age of 21 were enrolled on the multicenter AML02 study. This included 2 courses of intensive 3- or 4-drug induction timed by MRD-based risk stratification, followed by 3 courses of cytarabine-based consolidation that also included cladribine, etoposide, L-asparaginase, or mitoxantrone, depending on the cycle. All patients received CNS prophylaxis. Reported 3-year OS and EFS were 71% and 63%, respectively.

**Adult**

Most adult patients with AML are not treated on clinical trials. Approaches to treatment off trial are derived from studies published years ago, and further established as standards of care by consensus recommendations. “Younger” patients (in adults, usually defined as 18-60 years of age) who can tolerate intensive treatment are usually offered one course of induction chemotherapy (“7 + 3”) consisting of 3 days of an anthracycline and 7 days of continuous cytarabine (100-200 mg/m²). The addition of high-dose cytarabine to induction typically increases toxicity without improving complete remission (CR) rates. There have been no convincing improvements demonstrated by adding additional cytotoxic agents (such as 6-thioguanine). The benefit of granulocyte colony-stimulating factor priming is uncertain, with at least one study showing a disease-free survival benefit for favorable-risk patients. Postremission therapy typically consists of up to 4 courses of consolidative single-agent cytarabine, with a landmark CALGB study showing a dose effect favoring monthly high-dose ARA-C (HiDAC) in patients under the age of 60. Multi-agent chemotherapy has not been demonstrated to add significant improvement to cytarabine alone. CNS prophylaxis is usually not a part of adult protocols. Multiple studies have demonstrated the strong influence of pretreatment cytogenetics on outcomes with standard therapy. Allogeneic transplantation is often offered to patients with poor-risk cytogenetic features, with a recent meta-analysis also suggesting a benefit for intermediate risk patients in first complete remission (CR). CR rates in younger adults are in the range of 60%-80% with 5-year OS between 30%-50%. Interestingly, among clinical trial protocols internationally, there is significant heterogeneity in the treatment intensities offered to adults. The German AML cooperative group treats all enrolled adults with a double-induction strategy, and a pilot study by this group using sequential dose-dense S-HAM with pegiligrastim reported a 2-year OS of 69%-75% for patients with intermediate or favorable karyotypes. Similarly, the UK Medical Research Council (MRC) offers the same clinical trial backbone, which includes double induction and intensive consolidation, to all patients up to the age of 60, although patients over the age of 40 on a recent MRC trial demonstrated increased toxicity to more intensive therapy. In general, there appears to be a renewed interest in increasing the intensity of standard adult induction chemotherapy, as shown by a recent Eastern Cooperative Oncology Group (ECOG) study in which daunorubicin 90 mg/m² was superior to 45 mg/m² in adults under the age of 60.

**AYAs**

Unlike in ALL, there are few retrospective studies looking at the outcomes for AYAs treated on pediatric versus adult protocols. Side-by-side comparisons of representative differences in adult and pediatric AML strategies are shown in Tables 4-5. One initial effort comparing AYA outcomes on adult (CALGB and SWOG) versus pediatric (COG) studies was presented at the ASH annual meeting in 2010. In this retrospective study, which encompassed trials from 1986 to 2008, overall survival was noted to be significantly higher for the COG cohort than for the CALGB/SWOG cohort (45% vs 36%, P < .001). However, the COG AYA cohort (17.2 years) was younger than the CALGB (20.1 years) and SWOG (19.8 years) cohorts, which may have influenced these results. A separate study looked at patients under the age of 30 treated on the German AML-BFM 93/98, AMLCG 92/99, and AML SD HD 93/98A trials. Here, there were no differences in results from the pediatric and adult protocols for patients of similar ages, although the protocols were not that dissimilar. A third study, looking at outcomes from 2 institutions, found no difference in outcomes in patients up to the age of 21 treated on pediatric versus adult services, although these data spanned several years and included a variety of institutional protocols. There are no retrospective or prospective comparisons of AYAs treated with standard adult-like 7 + 3 induction and cytarabine consolidation versus intensive, pediatric-like strategies such as the St Jude AML02 study. Although treatment intensification appears to preferentially benefit younger patients with favorable prognostic features, the answer to whether AYAs with favorable cytogenetics fare better with pediatric-like rather than standard adult-like treatment remains unknown. Also unknown is whether intensive therapy in AYAs with intermediate-risk AML might render allogeneic HCT in first complete remission unnecessary.

**Special cases: FLT3 ITD**

The above discussion has addressed general treatment approaches for non-M3 AML, but 2 cases of particular contemporary interest deserve special mention. In both of these situations, several separate adult and pediatric trials are ongoing to define the roles of targeted therapies. The first involves “cytogenetically normal” AML with mutations identified in the FMS-like tyrosine kinase 3 (FLT3) gene. Activating internal-tandem duplication (ITD) mutations have been associated with particularly poor prognosis, and European LeukemiaNet recommendations include allogeneic
stem cell transplantation in first remission for patients with FLT3 ITD mutations. In recent years, however, several FLT3-tyrosine kinase inhibitors have been developed, and these are currently being tested in clinical trials. Data are emerging from combined chemotherapy/TKI phase 1/2 trials, and at least 6 phase 2/3 studies are ongoing in older and younger patient populations. There are no published data yet that prove the superiority of this approach to allogeneic stem cell transplantation in first complete remission for this poor-prognosis group. A second case that merits brief discussion is acute promyelocytic leukemia (APL). Unlike other subtypes of AML, complete remission rates are often greater than 90% with cure rates of almost 80%, an achievement made possible by the advent of all-trans-retinoic acid (ATRA) for this disease. Nonetheless, several treatment questions remain, including the role of arsenic trioxide (ATO) in induction or consolidation, the number of patients who are willing to undergo transplantation and have an available donor should at least be offered transplantation as a treatment strategy until or unless FLT3 TKI–containing chemotherapy is proven by ongoing studies to be an acceptable up-front alternative. Regarding APL, we believe that questions regarding appropriate induction, consolidation, and maintenance strategies should be studied similarly in both pediatric and adult clinical trials, and that patients should be referred for enrollment onto these trials whenever possible.

**Hodgkin lymphoma**

**Incidence**

Using US SEER data, annual rates for new diagnoses of Hodgkin lymphoma in the United States vary from 0.1-1.2/100,000 in children up to age 15, 2.9-4.3/100,000 in AYAs, and 2.4-4.5/100,000 in adults over the age of 40.

**Pediatric**

Between 85% and 95% of patients up to the age of 45 with new diagnoses of Hodgkin lymphoma are cured, including 93% to 98% of children. Protocols include several different variations of multi-agent chemotherapy with or without radiation, with examples and doses provided in Table 6. Pediatric studies are now focused on early risk stratification and tailored treatment strategies to minimize late effects. The COPP/ABV regimen reduces total cumulative doses of alkylators (risk of t-MDS), doxorubicin (risk of cardiac damage), and bleomycin (risk of pulmonary toxicity).

The Stanford V regimen includes only 12 weeks of treatment for high-risk patients and HLA-matched sibling available; alternative donors permitted. Protocols include several different variations of multi-agent chemotherapy with or without radiation, with examples and doses provided in Table 6. Pediatric studies are now focused on early risk stratification and tailored treatment strategies to minimize late effects. The COPP/ABV regimen reduces total cumulative doses of alkylators (risk of t-MDS), doxorubicin (risk of cardiac damage), and bleomycin (risk of pulmonary toxicity).
involved-field radiation therapy is used judiciously, and some groups are attempting to omit radiation altogether. In the POG-9425 study,69 216 patients under the age of 22 with intermediate- or high-risk Hodgkin lymphoma were treated with 3 courses of ABVE-PC every 21 days, an approach that exceeded the dose densities for doxorubicin and vincristine used in escalated BEACOPP70 but entailed lower cumulative doses of drugs than many regimens. Rapid early responders then received 21 Gy to involved regions, and slow early responders received 2 additional ABVE-PC cycles before radiation. Five-year OS for the entire cohort was 95% with 5-year EFS of 84%. Ongoing COG studies continue response-based treatment stratification, and many strategies do not include radiation. As most patients are treated off trial, physician factors including practice type and experience may play a significant role in the choice of initial therapy for many adult patients with Hodgkin lymphoma.71

AYAs

Table 6 provides examples of pediatric and adult trials for Hodgkin lymphoma that are being conducted in the United States. At least 2 retrospective studies have looked specifically at AYAs receiving care on adult protocols for Hodgkin lymphoma. One of these, from British Columbia, showed no difference in important presenting features between adolescents (16-21 years) and young adults (22-45 years), and reported encouraging 10-year progression-free survival (PFS) rates of 77%-80% with 10-year OS rates of 89%-91% for the entire cohort.72 A more recent, similar analysis looking at adult protocols in Germany reported 6-year PFS and OS estimates of 80% and 94% for adolescents (15-20 years), and 80% and 91% for adults (21-45 years), although regression analyses showed age to be a significant predictor for OS (P = .004) and secondary malignancies to be more common in young adults (P = .037).73 Together, these data show generally favorable outcomes for AYAs with Hodgkin lymphoma. Current adult and pediatric treatment protocols for Hodgkin lymphoma share many similarities, so comparing an “adult-like” with a “pediatric-like” approach may be less relevant in this disease. Nonetheless, among the different competing treatment regimens, it is not known whether ABVE-PC, ABVD, Stanford V-, or something else represents the optimal initial treatment for AYAs with Hodgkin lymphoma, or what is the most appropriate use of IFRT in this patient population. As overall survival rates are
generally high, the determination of “optimal therapy” would likely be guided by late-effect profiles among the different possibilities, as well as the relative efficacies of these different regimens in patients with the highest risk presentations.

Recommendations

There are no data available to suggest that any one regimen is clearly superior for the current treatment of AYAs with Hodgkin lymphoma. Many pediatric and adult cooperative groups have open trials that are investigating risk-adapted therapy and treatment de-escalation (or escalation) for early favorable or unfavorable responses. We strongly recommend that AYAs with newly diagnosed Hodgkin lymphoma are referred to and enrolled onto available studies. The accumulation of the resulting data will be critical to determining the optimal treatment regimen, based on responses and late-effect profile, for this patient population.

Non-Hodgkin lymphoma: diffuse large B-cell lymphoma and anaplastic large cell lymphoma

Incidence

Using US SEER data, annual rates for new diagnoses of NHL in the United States vary from 0.5-1.2/100 000 in children up to age 15, 1.8-7.2/100 000 in AYAs, and 10.5-116.4/100 000 in adults over the age of 40.

Pediatric

Non-Hodgkin lymphomas are uncommon in pediatric patients, accounting for approximately 7% of cancers in patients younger than 20 years. Among these, diffuse large B-cell lymphoma (DLBCL) accounts for 10%-20% of pediatric NHL, with incidence increasing in the second decade of life. DLBCL has often been included with other types of more aggressive lymphomas in pediatric protocols, and rituximab has not typically been part of standard therapy. In the FAB/LMB96 trial, 145 patients with DLBCL were treated with a COP (cyclophosphamide, vincristine, prednisone) prephase, followed by 2 inductions with COPADM (cyclophosphamide, vincristine, Adriamycin, high-dose methotrexate, intrathecal methotrexate), 2 consolidation courses with cytarabine and high-dose methotrexate, and a randomization to a maintenance course or not. Poor initial responders received more intensive treatment. In this trial, the 4-year EFS for patients with DLBCL was 92.7% and the randomizations to less therapy did not appear to impact results. BFM trials that include DLBCL similarly utilize a cyclophosphamide, high-dose methotrexate, cytarabine, and intrathecal chemotherapy approach with high-dose intensity during the first month of treatment, and also further intensify therapy for poor early responders. Anaplastic large cell lymphomas (ALCLs) are also uncommon in pediatric patients, accounting for 13% of pediatric NHL, and a variety of lymphoma-like and even leukemia-like protocols have been utilized. The POG treated 86 patients with ALCL on a 12-month multi-agent lymphoma protocol using induction followed by APO maintenance as well as intrathecal therapy; 4-year EFS and OS for ALCL patients were 72% and 88%, respectively. A recently published study included 217 ALCL patients up to the age of 22 treated on a protocol based on NHL-BFM 90, using 6 courses of induction chemotherapy (agents included dexamethasone, cyclophosphamide, intrathecal therapy, methotrexate, ifosfamide, cytarabine, and etoposide) with or without additional vinblastine; 2-year EFS and OS rates for the trial population were 71% and 94%, respectively.

Adult

A variety of prospective, randomized adult trials have compared repetitive CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy (usually 6 to 8 cycles given every 21 days) with several other anthracycline-based regimens in the treatment of DLBCL, with no other regimen showing clear improvements in remission rate or survival. More recently, rituximab has been shown to produce significant benefits when added to CHOP. In the MiNT trial, 824 patients with DLBCL who were younger than 60 years of age were randomized to 6 cycles of CHOP-like chemotherapy with or without rituximab; 3-year EFS and OS in the rituximab arm were 79% and 93%, respectively. Strategies under clinical investigation include increasing dose density (as in comparing R-CHOP-14 with R-CHOP-21) or using infusional regimens (as in comparing dose-adjusted R-EPOCH with standard R-CHOP). Adult standard of care for newly diagnosed DLBCL typically includes 6-8 cycles of R-CHOP-21-like therapy, with shorter courses and the addition of radiotherapy as possibilities for earlier-stage and/or bulky disease. For anaplastic large cell lymphoma, most adults are treated with multi-agent regimens including an anthracycline, such as CHOP.

AYAs

Important biologic differences exist between pediatric and adult DLBCL and ALCL, with pediatric patients more likely to have GCB subtype DLBCL and ALK+ ALCL, both of which are favorable prognostic features in these diseases. A large SEER-based study showed inferior outcomes for young adults with NHL (ages 20-29) in comparison with children (ages 0-19), with 75% of young adults and 85% of children alive at 5 years from diagnosis. However, the biologic features and treatment details for these patients were not known. There are no data available to suggest whether AYA patients with DLBCL or ALCL would benefit more from pediatric-like approaches to the treatment of these diseases or from standard adult R-CHOP– or CHOP-based chemotherapy.

Recommendations

Currently, standard of care for AYAs with DLBCL or ALCL who are not eligible for pediatric or adult studies includes either R-CHOP–like therapy (for DLBCL) or CHOP-like therapy with or without early autologous stem cell transplantation (for ALCL, depending on ALK positivity). Although there are biologic differences between pediatric and adult DLBCL and ALCL, it is intriguing that approaches to therapy for these diseases are markedly different when comparing pediatric trial and adult off-trial treatment settings. Further study to explore the upper age limits for the feasibility of intensive pediatric-like approaches for these diseases could be very helpful for this patient population.

Challenges for cancer care delivery in AYAs

Even if the optimal treatment plans for AYAs were to be clearly defined, several issues in this patient population present barriers to achieving the success rates seen in younger patients with hematologic malignancies.
Biology

Hematologic malignancies in AYAs are more likely to have unfavorable biologic features than the same diseases in children. The percentage of ALL patients with Philadelphia chromosome positivity increases with age, and among Philadelphia chromosome–negative patients, there are more unfavorable cytogenetic features and fewer favorable mutations in AYA patients. For example, an analysis of karyotypic data collected from more than 4000 childhood and adult ALL patients entered onto UK ALL treatment trials showed that good risk abnormalities such as high hyperdiploidy and the t(12;21)(p13;q22) translocation were more commonly found among younger patients, whereas iAMP21 and IGH translocations were found more commonly in older children and adolescents. Additionally, older children and young adults appeared to be more likely to have unspecified chromosomal abnormalities. Data from the MRC UKALL/XII/ECOG2993 study demonstrate that cytogenetic subgroups other than the Philadelphia chromosome continue to have prognostic import in adult ALL. Similar findings were demonstrated in an analysis of patients ages 15-65 on the SWOG-9400 study. In AML, multiple studies demonstrate the prognostic importance of pretreatment cytogenetics in both pediatric and adult cohorts. In a recent analysis of data from the German AML-BFM 93/98, AMLCG 92/99, and AMLDG HD93/98A studies, investigators found that favorable cytogenetic profiles (t(8;21) and inv(16)) were found more commonly in patients ages 2-13 (32%) than in adolescents (25%) and young adults (22%). On the other hand, complex karyotypes were found more commonly in young adults (8%) than in adolescents (5%) or younger children (3%). Even in the absence of known prognostic cytogenetic differences, the inferior outcomes of AYAs relative to children on similar protocols in this study suggested that unmeasured age-related biologic changes were also important factors.

In a recent Hodgkin lymphoma retrospective analysis of adolescents and young adults (ages 21-45) treated on GHSG studies HD4 to HD9, the distribution of histologic subtypes included 49.8% nodular sclerosing, 12.8% mixed cellular, 3.7% lymphocyte-predominant/lymphocyte-rich, and 0.7% lymphocyte-depleted. The distribution of histologic subtypes in adolescents appeared to mirror the overall group. In contrast, earlier studies in pediatric Hodgkin cohorts have shown a higher proportion of patients with mixed cellular and lymphocyte-predominant histology; taken together, this suggests that the adolescents in the GHSG study may have had more biologic similarities to adults than children, and lends support to the concept of biologic age-related differences in this disease. As previously noted, proportions of GCB subtypes among DLBCL cases are higher in children. In an analysis of 63 pediatric patients (up to 18 years of age) on the NHL-BFM 90 and 95 trials, investigators classified 43 of 52 evaluable cases as belonging to a GCB subtype by immunohistochemistry. These investigators further noted that in comparison with their own data on adult DLBCL, pediatric DLBCLs were significantly more likely to belong to a GCB subtype than adult DLBCLs (P < .001). In an earlier series, it had been noted that pediatric DLBCLs were more likely to be of the centroblastic variant than adults (83% vs 75%), were more likely to be of a “monomorphic centroblastic variant” (63% vs 21%), and less likely to be of an immunoblastic variant (7% vs 15%). Finally, with regard to ALCL, Gascoyne et al looked at clinical and laboratory findings in 70 adults with systemic ALCL who were treated with curative intent. In this study, the median age of patients with ALK+ variants was significantly younger than for patients with ALK− variants (30 vs 61 years, P < .002), and ALK positivity independently predicted for overall survival. These observations again suggest important biologic differences in younger versus older patients with non-Hodgkin lymphomas.

Toxicities of treatment

Ongoing AYA ALL protocols as well as the AML trial experience in European groups have demonstrated the feasibility of delivering highly intensive “pediatric-like” treatment to AYAs. Nonetheless, toxicities increase with age. Toxicities in AYAs may be related in part to age-related differences in body mass index, hormones, and other factors. In the pediatric AIEOP-ALL 95 trial, the incidence of osteonecrosis was significantly higher in the older part of the cohort, with a peak incidence of 7.4% (compared with 1.6% in the entire cohort); this effect was also seen in the ALL-BFM 9599 and other studies. Children older than 10 years were significantly more likely to experience thromboembolic events on DFCI ALL protocols (44%) than younger children (4%), although this was in part related to higher doses of steroids in high-risk patients. Age has also been shown to be an independent risk factor for tumor lysis during ALL induction (in one study, 43% of patients age > 10 experienced tumor lysis syndrome vs 23% overall), as well as diabetic ketoacidosis (out of 797 evaluable patients in one study, 4 of 6 who experienced this condition were > age 10) and hyperglycemia more generally. Children older than 16 years were more likely to experience microbiologically documented infections on the CCG-2961 AML trial (hazard ratio 3.32), and children older than 10 years had higher rates of fungal infection after either intensive consolidation or transplantation on CCG-2891 (incidence rate ratio 2.763). In the AML-BFM 93 and AML-BFM 98 trials, age older than 10 years was associated with higher treatment-related mortality between days 15 and 42 (10.6% in age > 10 vs 8.0% overall), and at St Jude, age was demonstrated to be a risk factor for AML treatment-related adverse events (4.3% increase per year of age in the recent era) as well as death during induction therapy and death in first remission in both ALL (5.8% cumulative incidence of death in patients age > 10 vs 1.6% in patients ages 1-9) and AML (12.4% cumulative incidence of death in patients age > 10 vs 2.3% in patients ages 1-9). Obesity is more common in AYAs than in younger children, and has been independently associated with treatment-related toxicity in AML. An analysis of COG data concluded that age should be used to define risk for pediatric malignancies in a manner dependent on the morbidity of the considered treatment. The association of age with toxicity in adults undergoing intensive treatment is well documented, with a representative analysis showing a clear relationship between AML induction-related serious adverse events or mortality with age older than 60 (in this study, 21% induction mortality in patients aged > 60 vs 10% in patients aged < 60). Nonetheless, highly intensive approaches in younger adults are feasible.

Access and site of care

AYAs can be seen by either pediatric or adult oncologists for initial treatment. A study from the Utah Cancer registry showed that 47% of older adolescents with leukemia and 71% with lymphoma did not see a pediatric oncologist, and of those treated by adult oncologists, 72% were treated outside of an academic center. In Georgia, 36% of patients between the ages of 15 and 19 were treated at a COG institution, and 5-year actuarial survival rates for ALL were higher than for those not treated at a COG institution.
(86% vs 53%, \( P < .05 \)).\(^{112}\) Similar data from Ohio showed that 47% of cancer patients between the ages of 15 and 19 were treated at a pediatric center, 25% at adult academic centers, and 29% at community hospitals.\(^{113}\) A study from Canada showed that 30% of adolescents were seen at a pediatric center.\(^{114}\) Underinsurance and uninsurance have been significant problems for AYAs. In a US study of 270 AYAs, having public or no health insurance was associated with a 13-week delay in diagnosis relative to having private insurance.\(^{1}\) Differences in insurance were hypothesized to be partly responsible for the inferior outcomes of AYAs on CALGB versus CCG trials.\(^{115}\) Low socioeconomic status was associated with reduced OS and NHL-specific survival among AYAs in a California cancer registry study.\(^{116}\)

### Transition to adult care setting

Different expectations are placed on AYAs within pediatric versus adult health care systems in terms of the “role” of the patient,\(^{117}\) an issue highlighted by the literature about “transition” from pediatric to adult health care for children with chronic diseases such as cystic fibrosis\(^{118}\) and congenital heart disease.\(^{119}\) A recent study of participants with sickle cell disease in the Dallas Newborn Cohort found that although most children (94%-98%) lived to become adults, transition to adult health care was associated with a higher risk of death.\(^{120}\) Within oncology, transition issues are most obvious for survivors of childhood cancer who move into adult health care settings.\(^{121}\) Nonetheless, because “successful” transition includes meeting the specific developmental needs of a young population, this has implications for the design and implementation of treatment settings for AYAs with active malignancies.\(^{122}\)

### Access to clinical trials

Whether AYAs are seen in pediatric or adult settings, clinical trial enrollment for this population is lower than for younger or older patients.\(^{4,123}\) In Northern England, 92% of 0- to 14-year-olds with leukemia were enrolled onto a clinical trial, compared with 60% of patients between the ages of 15 and 24 years.\(^{124}\) Throughout England, overall accrual rates for all patients with new malignancies between 2005-2007 were 25% for 15- to 19-year-olds and 13% for 20- to 24-year-olds,\(^{125}\) with another study estimating an enrollment rate of 8% among 35- to 39-year-olds.\(^{126}\) A study at the Children’s Hospital of Pittsburgh and the University of Pittsburgh Cancer Institute showed that 26% of AYA patients with new cancer diagnoses at the pediatric center were enrolled on a trial,\(^ {127}\) and 4% of those seen at the adult center were placed on trials.\(^ {128}\) Throughout the United States, it is estimated that 2% of cancer patients between the ages of 20 and 29 enter trials.\(^ {129}\) Hypotheses vary but could be because of lack of available clinical trials, reluctance of physicians to offer clinical trials to this group of patients, or higher rates of patient refusal.

### Adherence to medications and treatment plans

Critical to the outcomes of AYAs with cancer is the ability of these patients to receive all medications and treatments prescribed, which is in part mediated by adherence.\(^ {130}\) Empiric data suggests that AYA patients with ALL and Hodgkin lymphoma are suboptimally adherent to prescribed cancer therapy.\(^ {130}\) It is estimated that up to 63% of AYAs with cancer may not fully adhere to treatment regimens.\(^ {3}\) Nonadherence tends to be compounded in AYAs because of factors\(^ {131}\) such as growing independence, transition away from parental involvement, financial problems, competing life obligations, and lack of social support. In diseases such as chronic myeloid leukemia (not specifically discussed in this review), treatment is daily and lifelong, and nonadherence rates are estimated to be as high as 33%.\(^ {132}\) Adherence to tyrosine kinase inhibitor (TKI) therapy has been found to be associated with levels of molecular response in this disease.\(^ {133}\) For AYAs with newly diagnosed CML, challenges with medication adherence over potentially many years of therapy might have important effects on survival.

### Other psychosocial considerations

Psychosocial issues in AYAs with cancer\(^ {134}\) can be because of family factors (including amount of parental involvement, or conversely raising a family with young children at home),\(^ {135}\) psychological/emotional challenges (cognitive development, educational attainment, available coping strategies, psychological resiliency), and social concerns (peer relationships and support, romantic relationships, job and financial security). Distress and psychosocial challenges among AYAs may be poorly identified by treatment providers.\(^ {136}\) Psychological issues during treatment impact adherence, as discussed previously, as well as the potential for posttraumatic stress during cancer survivorship.\(^ {137}\) Young adults with chronic conditions are at least as likely as peers to engage in risky behaviors,\(^ {138}\) which might also affect cancer treatment outcomes. AYAs with cancer are likely to report specific information and assistance needs (such as around diet and nutrition, fertility options, complementary and alternative therapies, and health insurance), which often go unmet.\(^ {139}\) Fertility considerations are recognized as increasingly important in cancer patients\(^ {140}\) and may impact choices of anticancer therapy or the use of fertility preservation techniques. In some instances in which therapy is continuous and ongoing, as in CML, AYAs may want to explore the possibility of interrupting or continuing treatment while becoming pregnant and having children. This remains a relatively understudied area.\(^ {141}\)

### Observations and future research

AYAs are a particularly high-risk group among patients diagnosed with cancer, and this review has addressed some of the issues associated with AYAs with hematologic malignancies. With these challenges come opportunities. Our observations about approaches that might be used to study and improve outcomes in the AYA population are summarized here and shown in Table 7.

#### 1. Collect and analyze data to form hypotheses regarding optimal treatment strategies for AYAs and to guide treatment...
planning. “Rapid learning cancer care,” the subject of a recent National Cancer Institute and Institute of Medicine workshop, is a concept characterized as the use of “real-time clinical data to drive the process of scientific discovery, which becomes a natural outgrowth of patient care.”142 By creating continuously updated repositories of patient-level AYA data on and off pediatric and adult trials, this type of approach could be used to ask and answer the following questions: What percentages of AYA patients receive which kinds of treatments for the major hematologic malignancies, and where? For patients matched for known prognostic factors, which kinds of treatments for the major hematologic malignancies, following questions: What percentages of AYA patients receive trials, this type of approach could be used to ask and answer the repositories of patient-level AYA data on and off pediatric and adult

that AYA Ph ALL trials have demonstrated the feasibility of extending intensive pediatric-like treatment approaches to young adults, as have some European cooperative group trials in AML. By moving past the typical pediatric upper age limit toward “age-unrestricted” approaches, trialists may be able to more carefully explore the biologic age-based limits of treatment tolerance and toxicity. In contrast, for some diseases, intensive treatment strategies for AYAs may not be necessary to produce optimal results. Age-unrestricted trials for AYAs may also permit careful study of the late-effect profiles of the usual pediatric and adult approaches. These approaches do not necessarily have to utilize novel agents and require large amounts of external funding, but could be designed mainly to determine whether pediatric or adult “standard-of-care” approaches are more appropriate for younger adults. An alternate approach to adding AYAs onto pediatric trials would be to open trials specifically for AYAs that look at pediatric- vs adult-inspired standard treatment approaches.

2. Open sequential clinical trials designed for AYAs. Analogous to the US phase 2 intergroup trial for AYAs with Ph ALL, trials might be opened for AYAs with other major hematologic diseases. The AYA Ph ALL trials have demonstrated the feasibility of extending intensive pediatric-like treatment approaches to young adults, as have some European cooperative group trials in AML. By moving past the typical pediatric upper age limit toward “age-unrestricted” approaches, trialists may be able to more carefully explore the biologic age-based limits of treatment tolerance and toxicity. In contrast, for some diseases, intensive treatment strategies for AYAs may not be necessary to produce optimal results. Age-unrestricted trials for AYAs may also permit careful study of the late-effect profiles of the usual pediatric and adult approaches. These approaches do not necessarily have to utilize novel agents and require large amounts of external funding, but could be designed mainly to determine whether pediatric or adult “standard-of-care” approaches are more appropriate for younger adults. An alternate approach to adding AYAs onto pediatric trials would be to open trials specifically for AYAs that look at pediatric- vs adult-inspired standard treatment approaches.

3. Establish academic AYA centers of excellence to facilitate community referral and clinical trial enrollment. Although several institutions have begun to develop AYA programs,122 the incentives for clinicians to refer from community practices will be stronger if AYA-directed trials are available and open at these centers. With such infrastructure in place, barriers to AYA clinical trial enrollment can be more meaningfully studied.

4. Implement patient navigators with AYA expertise. AYAs confront several psychosocial barriers to full receipt of appropriate care, as described in this review. A patient navigator143 with AYA expertise might be trained to recognize and address these barriers (such as underinsurance, adherence, social support, and other issues) by connecting AYAs with strategies and resources. The internet connectedness and social networking tendencies of AYAs may provide a rich resource to further identify and understand psychosocial issues.145,146 By studying and recording the experiences of patient navigators working with this population, the effects of this support on clinical outcomes could be quantified and future approaches to psychosocial support in this population could be further optimized.

These observations are a starting point for strategies that might improve the outcomes of AYAs with hematologic malignancies. Although directed toward AYAs, these principles are applicable broadly to many patients receiving cancer care, such as learning from real-time data, comparing competing standard-of-care treatment approaches, and tailoring patient navigation to the needs of specific populations. AYAs with cancer represent an important opportunity to improve overall cancer care.

Authorship

Contribution: W.W. designed research, performed research, analyzed data, and wrote the paper; and S.J.L. designed research, interpreted data, and critically analyzed the manuscript.

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