Unique Characteristics of Adolescent and Young Adult Acute Lymphoblastic Leukemia, Breast Cancer, and Colon Cancer

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Each year in the United States, nearly 70,000 individuals between the ages of 15 and 40 years are diagnosed with cancer. Although overall cancer survival rates among pediatric and older adult patients have increased in recent decades, there has been little improvement in survival of adolescent and young adult (AYA) cancer patients since 1975 when collected data became adequate to evaluate this issue. In 2006, the AYA Oncology Progress Review Group made recommendations for addressing the needs of this population that were later implemented by the LIVESTRONG Young Adult Alliance. One of their overriding questions was whether the cancers seen in AYA patients were biologically different than the same cancers in adult and/or pediatric patients. On June 9–10, 2009, the National Cancer Institute (NCI) and the Lance Armstrong Foundation (LAF) convened a workshop in Bethesda, MD, entitled “Unique Characteristics of AYA Cancers: Focus on Acute Lymphocytic Leukemia (ALL), Breast Cancer and Colon Cancer” that aimed to examine the current state of basic and translational research on these cancers and to discuss the next steps to improve their prognosis and treatment.

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One reason that there has been less progress in treating cancers among adolescents and young adults might be that the biology is different from the same diseases in younger and older individuals. The Progress Review Group on adolescent and young adult (AYA) oncology recommended that we improve the “understanding of host/patient biology of aging and cancers, including sarcomas, leukemias, lymphomas, and breast and colorectal carcinomas” and investigate a “potential biological basis of age-related differences in outcome for AYA cancers.” As a result, the Bethesda workshop was organized to review and update the status of AYA research in these cancers and to consider whether there is sufficient evidence for a unique biology in these AYA cancers to distinguish them from the adult and (in the case of acute lymphocytic leukemia [ALL]) pediatric versions of the disease. We hoped to gain a better understanding of AYA cancers and to identify new therapeutic targets and treatment approaches for AYA patients.

AYA Acute Lymphoblastic Leukemia

Acute lymphoblastic leukemia is one of the leading causes of cancer-related deaths among adolescents and young adults. Overall survival and disease-specific survival of ALL are clinically significantly poorer in AYA patients than in children between 1 and 10 years of age. It is not known whether these outcome differences are due to distinct genetic and biological features, different therapeutic regimens and intensities, differences in compliance to therapy, or other social and behavioral issues (Table 1).

Dr Cheryl Willman (University of New Mexico Cancer Research and Treatment Center) discussed evidence that outcomes among pediatric ALL patients vary depending on the presence of various recurring cytogenetic abnormalities. ALL patients with “good” prognosis cytogenetics (such as trisomies of chromosomes 4, 10, or 17, or t(12;21)/TEL-AML1) had relatively high survival rates, whereas those with other recurring abnormalities had intermediate or poorer outcomes (1). Substantial differences existed in the frequencies of various cytogenetic abnormalities among AYA patients compared with younger ALL patients, including a precipitous decline in the frequency of the “good prognosis” abnormalities by approximately 20 years of age. The “poor prognosis” abnormalities, such as t(9;22)/BCR-ABL, were more common in AYA ALL (2). Under the auspices of the National Cancer Institute’s (NCI’s) Strategic Partnering to Evaluate Cancer Signatures (SPECs) program and its Therapeutically Applicable Research to Generate Effective Treatments (TARGET) project, Willman and colleagues recently completed gene expression profiling studies to identify and characterize novel genetic abnormalities and therapeutic targets in a cohort of 207 older children with “high-risk” ALL (mean age = 13.5 years, with white blood cell counts higher than 50,000/mm³ at presentation) who had been treated on the Children’s Oncology Group (COG) 9906 protocol. Gene expression clustering algorithms revealed eight gene expression cluster groups, two of which were associated with distinct cytogenetic abnormalities [11q23 rearrangements MLL or t(1;19) E2a-PBX1] and six of which were entirely novel, in which the underlying genetic abnormalities were unknown. One of the novel clusters, which represented 12%–15% of all high-risk ALL cancers studied in this series, was characterized by high expression of CRLF2, GPR110, MUC4, and other genes associated with activated...
tyrosine kinases, and frequent deletions of **IKZF1**, **BTLA/CD300**, **RAG1-2**, and **EBF1**. It was also associated with Hispanic or Latino race 

\[ P = .001 \] and with very poor 4-year relapse-free survival (21%, \( P < .001 \)) (3–7). Because these gene expression profiles were characteristic of activated tyrosine kinase pathways, some kinases were resequenced, leading to the discovery of novel Janus kinase 2 (\( JAK2 \)) and other kinase mutations in this high-risk form of the disease. These studies suggest that perturbation of these signaling pathways, along with \( IKZF1 \) deletion, cooperate to promote leukemogenesis. Early phase clinical trials to test JAK inhibitors in patients with high-risk ALL are ongoing (3). Dr Willman noted that in preliminary studies, AYA ALL cancers appeared to be genetically similar to high-risk pediatric ALL. Working with the NCI adult cooperative groups, the TARGET cohort is being expanded to include 400 AYA ALL patients (NCI IR1C1 CA145707; Willman and Mullighan, principal investigators).

Treatment failure remains a major problem in the management of pediatric, adolescent, and young adult ALL. The genetic basis of treatment failure is particularly poorly understood in the AYA population because it often occurs in patients lacking known high-risk alterations such as **MLL-rearrangement** or **BCR-ABL1**. Dr Charles Mullighan (St Jude Children’s Research Hospital) presented the results of an integrated genomic analysis of B-cell precursor (BCP) samples that lacked known high-risk genetic alterations from a cohort of high-risk pediatric and adolescent ALL patients (COG P9906 cohort). They identified deletions and point mutations of the lymphoid transcription factor **IKZF1** that were associated with a nearly threefold increased risk of relapse (hazard ratio = 2.40; 95% confidence interval = 1.38 to 4.2). The gene expression signatures of these patients were very similar to those of **BCR-ABL1** ALL patients, and by resequencing, activating mutations of Janus kinases (\( JAK1 \), \( JAK2 \), and \( JAK3 \)) were identified in 11% of the cohort. The mutated JAK kinases could transform cells in vitro, were responsive to JAK inhibitors, and were associated with very poor outcome when combined with **IKZF1** deletions. When analysis was restricted to the adolescent ALL cases (\( N = 58; 16–21 \) years of age), similar results were found: 50 of these patients lacked a sentinel chromosomal alteration; however, they had a high frequency of JAK mutations and **IKZF1** deletions, and in 5 years, there was a 71% incidence of a recurrence in patients harboring both lesions as compared with 18% incidence in patients with neither lesion.

Although much is known about the genetics of childhood ALL, data are limited for AYA ALL. Dr Christine Harrison (Northern Institute for Cancer Research at Newcastle University) described the UK’s Leukaemia Research Cytogenetics Group database, which includes cytogenetic information and records of treatments on 1205 AYA patients, aged 13–24 years (8). Nearly 500 of these patients were treated on adult ALL clinical trials. Analyses of overall survival and event-free survival (EFS) revealed that AYA patients of the same age had worse outcomes when treated on an adult ALL protocol vs a pediatric ALL protocol. Of this group of patients, 432 were aged 13–14 years, 544 were aged 15–19 years, and 229 were aged 20–24 years; 63% were young men. Most patients had **BCP-ALL** (79%) and 21% had **T-lineage ALL**. The incidence of T-lineage, ALL-specific cytogenetic abnormalities varied among children, AYAs, and adults. For example, the **CALM-AF10** translocation occurred more frequently in AYAs than in children or adults. Of the 837 AYA patients in this group who had **BCP-ALL** there were more 13–24 year olds with \( t(4;11) \) (q21;q23) translocations (4%) than children aged 1–12 years with the same translocation (2%). Greater than 50% of AYA **BCP-ALL** patients had a visible abnormality of chromosome arm 9p, whereas other AYA **BCP-ALL** patients exhibited trisomies of chromosomes 21, 8, or 5. Trisomy 5 as a sole cytogenetic change has previously been associated with a poor outcome (9). Intrachromosomal amplification of chromosome 21 (iAMP21) has an incidence of about 3% in older children with ALL (median age 9 years) and accounts for 5% of AYA (10); it is associated with BCP immunophenotype and low white blood cell count. Data from the Medical Research Council ALL97 trial revealed that patients with iAMP21 had very poor EFS and experienced both early and late relapses. However, the overall patient survival was relatively good (5-year EFS was 29%, whereas overall survival was 71%) following treatment for their relapsed disease (11). Currently, these patients are being treated as at high risk in the Medical Research Council ALL2003 childhood ALL trial. Other translocations observed in **BCP-ALL** involve the immunoglobulin heavy chain locus (\( IGH @ \)) and are

### Table 1. Special features of cancers in adolescent and young adult (AYA) patients

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute lymphocytic leukemia</strong> (AYA patients)</td>
<td>Higher incidence of poor prognostic cytogenetic features such as ( t(9;22) ) (Philadelphia Chromosome) or hypodiploidy. Lower incidence of favorable cytogenetic features associated with a favorable outcome such as high hyperdiploidy and ( t(12;21) ) ETV6-RUNX1 translocation.</td>
</tr>
<tr>
<td><strong>Breast cancer in AYA patients</strong></td>
<td>Lower survival rate. Worse outcome independent of stage, extent, or type.</td>
</tr>
<tr>
<td><strong>Colorectal cancer in AYA patients</strong></td>
<td>Higher frequency of microsatellite instability.</td>
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</tbody>
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**Note:** The text above is a natural language representation of the document content, focusing on key findings and implications for treatment in adolescent and young adult patients with leukemia. Further details and analyses are presented in the referenced studies and databases.
seen more frequently in older children and adolescents as compared with younger children (12–15).

Dr Wendy Stock (University of Chicago) described the challenges of treating ALL in the AYA population. Older adolescents and young adults with ALL (16–21 years of age) have worse outcomes (7-year EFS = 34%) than children at 1–10 years of age for whom the cure rate now approaches 80%–85%. A retrospective comparison of 16–20 year olds with ALL who were treated on the Children’s Cancer Group (CCG) or Cancer and Leukemia Group B (CALGB) ALL protocols revealed that despite similar remission rates between the two treatment groups, there was a statistically significantly lower 7-year EFS among those participants treated on the CALGB protocol as well as a higher rate of central nervous system relapse (16) (7-year EFS = 63% [CCG AYAs] vs 35% [CALGB] AYAs; relative incidence ratio = 9.2, 95% confidence interval = 2.0 to 42.7; P < .001). Compared with adult protocols, the pediatric protocols featured substantially more nonmyelosuppressive therapy (vincristine, corticosteroids, and l-asparaginase) elements and more intensive early CNS-directed therapy. Similar results have been observed in retrospective analyses of AYA patients in France, the United Kingdom, and the Netherlands; nearly identical remission rates were observed, but EFS and survival were substantially better for AYA patients enrolled on the pediatric trials (67% vs 41% 5-year EFS in France; 71% vs 56% 5-year overall survival in the United Kingdom, and 71% vs 38% 5-year EFS in the Netherlands) (17–19).

Explanations for these striking differences include potential, clinical, and biological differences among adolescents who received treatment at pediatric centers compared with adult centers, differences in protocol design and dose intensity, and potential variations in the degree of adherence to the protocol drug administration by medical oncologists and their patients compared with pediatric oncologists and by their patients. To address many of these unanswered questions, the adult cooperative groups are performing a prospective trial that focuses specifically on AYAs (Intergroup trial C10403). Newly diagnosed ALL patients between ages 16 and 40 years are eligible for treatment that parallels the current COG study for adolescents and high-risk children (AALL0232).

Asparaginase, which deprives the leukemic cells of asparagine that is essential for growth, is considered to be part of the standard treatment in pediatric ALL protocols. However, because of toxicity and limited tolerability in older adults, medical oncologists do not routinely use it. Since 1973, the Dana-Farber Cancer Institute ALL Consortium has conducted randomized multi-institutional clinical trials for children up to 18 years of age with newly diagnosed ALL. Older adolescents (15–18 years old) have been treated as high-risk, and postinduction consolidation (follow-up therapy after the induction of remission in the patient) has focused on continuous asparagine depletion by administration of asparaginase for 20–30 weeks. Fifty-one patients aged 15–18 years were treated in two consecutive Dana-Farber Cancer Institute ALL Consortium trials. Compared with patients aged 1–10 years, older adolescents experienced more thromboembolic complications (2% in 1–10 year olds vs 14% in 10–15 year olds vs 10% in 15–18 year olds, P < .01) but had similar rates of pancreatitis and asparaginase allergy. The 5-year EFS for these older adolescents was 78%. Based on this favorable outcome, Dr Lewis Silverman (Dana-Farber Cancer Institute) described a pilot study that was initiated to determine the feasibility of administering the Dana-Farber Cancer Institute pediatric regimen to young and middle-aged adults between 18 and 50 years of age (20). Preliminary results suggest that an asparaginase-intensive pediatric regimen is feasible in older adolescents (aged 15–18 years) and young adults (aged 18–50 years) with ALL.

**AYA Breast Cancer**

Breast cancer is the second most common cause of cancer-related death for women in the United States and is the leading cause of cancer death for young women aged 15–29 years. Younger women with breast cancer exhibit an increased likelihood of recurrence and death compared with older premenopausal women, and young age is itself an indicator of poorer survival. Although multiple factors may contribute to these differences, the goal of this Workshop was to address the hypothesis that a unique biology may underlie the distinctive properties of breast cancer in adolescent and young adult women (Table 1).

Dr Christopher Benz (Buck Institute for Age Research) noted that the link between breast cancer and aging is poorly understood and that late-onset breast cancers are more likely to overexpress estrogen receptor (ER)-α and progesterone receptor (PR), whereas breast cancers in women younger than 40 years are more likely to be “triple-negative,” lacking overexpression of ER, PR, and HER2. Biomarkers like HER2 and Ki-67 are inversely associated with ER expression and appear to be more commonly associated with early-onset breast cancer (21).

In studies of differences in gene expression among women of different ages with breast cancer, early-onset ER-positive breast cancers were more proliferative and more likely to result in metastatic relapse compared with stage-matched ER-positive breast cancers that arose after age 40 years. A comparison of node-negative breast cancers that were diagnosed in women aged 70 years or older with those that were diagnosed in women younger than age 45 years revealed differences in gene expression microarray profiles but no age-associated genomic differences (22). ER-negative breast cancers proliferated faster than ER-positive breast cancers and were associated with greater risk of early metastatic relapse regardless of age at diagnosis. For ER-negative breast cancer, better biomarkers are needed to predict patient outcome and treatment responsiveness, and more studies are needed to evaluate the biological heterogeneity of early-onset ER-negative breast cancers in different ethnic populations.

Dr Thea Tlsty (University of California, San Francisco; UCSF) emphasized that premalignant breast tissue also exhibits specific molecular subtypes that may give clues to targeting treatment. Ductal carcinoma in situ (DCIS) is a nonobligate precursor of invasive breast cancer, and 50% of DCIS patients do not go on to develop invasive cancer. Although DCIS is relatively rare in young women, the tendency to reoccur is higher in this population. The UCSF DCIS Clinical Cohort Study identified biomarkers in the lesions of women with DCIS that can predict future diagnosis of invasive breast cancer (23), and a molecular signature in which high levels of p16 and low levels of Ki67 expression were associated with recurrence-free survival. High levels of p16-regulated proliferation markers (E2F and cyclin E1) and cyclooxygenase-2...
Commentary

Tlsty emphasized the need for specific predictive tests for basal-like DCIS cancers to alleviate women’s anxiety regarding treatment and prognosis that accompanies this diagnosis. Dr. Tlsty also described new studies that identified rare subpopulations of breast epithelial cells that have properties of stem cells or premalignant cells and suggested that premalignant cells might be good treatment targets in young women.

Dr. Carey Anders (University of North Carolina, Chapel Hill) explained that although the risk of breast cancer is lower in younger women, survival of women aged 25–30 years is lower across all subtypes and stages (24). However, risk factors associated with premalignant breast cancer (obesity, high caloric intake, sedentary lifestyle, early age at menarche, heavy alcohol intake, high intake of red meat, and high breast density) are not exclusive to early-onset breast cancer. Early-onset tumors were associated with family history of the disease, a more aggressive phenotype, ER- and/or PR-negative status, and compared with tumors in women older than age 30 years, were larger and more often associated with positive lymph nodes and higher levels of HER2 expression.

Dr. Anders and her collaborators compared gene expression, clinicopathologic features, and oncogenic pathway deregulation in more than 700 tumors according to patients’ ages. They confirmed differences in pathology and mRNA expression of ER, PR, HER2, and the epidermal growth factor receptor (25) and that diagnosis at an age younger than 45 years was the strongest predictor of poor prognosis. Compared with tumors in older women, tumors from young women had multiple clusters of differentially expressed genes, including a higher probability of phosphatidylinositol-3 kinase and Myc pathway deregulation (26). Such differences may underlie the clinical and prognostic differences in early-onset breast cancer. Dr. Anders noted that among pre- and postmenopausal women with breast cancer who have been treated similarly, younger women with stage I or II cancers are twice as likely to suffer local recurrence following lumpectomy and radiation than older women, so there is a need for improved individualized strategies for both local and systemic therapy for young women.

Dr. Christine Ambrosone (Roswell Park Cancer Institute) reported that European American women have higher incidence of breast cancer than African American women, and premenopausal women of both races develop a higher proportion of basal-like tumors than postmenopausal women (27). African American women are more likely than white women to be diagnosed before age 40 years with more aggressive basal-like tumors (28,29).

Data from the Women’s Circle of Health Study (30) confirmed that ER-negative tumors were more common among African American women than among white women, particularly when younger women were compared. Also, regardless of race, women younger than age 40 years were more likely than women aged 40 years and older to have high-grade tumors. Genome-wide association studies have suggested that different genes are associated with breast cancer in African American women compared with European American women, but age-stratified data are needed.

Dr. Charlotte Kuperwasser (Tufts University School of Medicine) described her human-in-mouse model in which human stromal cells, epithelial cells, and primary fibroblasts from a reduction mammoplasty are used to generate human breast tissues that organize both structurally and functionally in mice (31,32) and are virtually indistinguishable from breast tissue taken directly from humans (33). She also discussed ER-negative breast cancer, its association with age of breast cancer onset, and the role of estrogen in breast cancer formation and progression. Estrogen accelerated the growth of ER-negative tumors in a mouse model of pregnancy-associated breast cancer, and it also accelerated tumor formation by ER-negative human breast, prostate, and colon cancer cell lines (34). In mice, estrogen increased angiogenesis—increasing the number and size of blood and lymphatic vessels, stromal cells, and the incidence of metastasis—and stimulated cells in the bone marrow to mobilize to sites of angiogenesis (34). Tumors that arose during times of high circulating estrogens apparently lacked the ability to respond directly to the hormone, suggesting that estrogen may work indirectly to promote cancer in younger women (34).

**AYA Colon Cancer**

It has been known for the last two decades that AYA patients with colorectal cancer have a poorer prognosis and more aggressive disease than older adults (35). However, the biological basis and the clinical ramifications of this observation remain incompletely defined. Some of the best evidence that colorectal cancer is biologically different in AYA patients compared with older adults includes diagnosis at a more advanced tumor stage, greater frequencies of mucinous histology, signet ring cells, high microsatellite instability (MSI-H), and a higher incidence of mutations in one of the mismatch repair (MMR) genes that results in its constitutive expression (36–40) despite some evidence to the contrary (41). In addition, there are lower frequencies of KRAS mutations, loss of heterozygosity at 17p and 18q, and lower p53 protein levels in AYA colorectal tumors (Table 1).

Dr. Sharon Plon (Baylor College of Medicine) discussed genetic susceptibility syndromes that are associated with an increased risk of developing colorectal cancer in AYA populations. Familial adenomatous polyposis is an autosomal dominant condition in which polyps can begin to develop in the first decade of life, extensive polyposis with atypia may be present during the teen years, and frank invasive carcinoma often develops in young adults (42). The lifetime cumulative risk of colorectal cancer is virtually 100% for familial adenomatous polyposis patients, with a cumulative risk of approximately 50% by age 33. Familial adenomatous polyposis is caused by the presence of germline heterozygous mutations of the APC gene, of which approximately 80% are predicted to truncate the APC protein. Approximately 80% of all colorectal tumors exhibit chromosomal instability that is associated with either inherited or somatic mutation of the APC gene. Chromosome instability is less frequently observed in AYA than in adult colorectal cancer, and AYA tumors are more likely to exhibit microsatellite instability (40).

Dr. Plon pointed out that hereditary nonpolyposis colorectal cancer (HNPCC, also called Lynch syndrome) is an autosomal...
dominant syndrome without polyposis that is associated with an approximately 70% lifetime risk of colorectal cancer (often right-sided) and a 50%–70% risk of endometrial cancer (42). The autosomal dominant form is caused by heterozygous mutations in one of four MMR genes (MSH2, MLH1, MSH6, or PMS2) and is associated with colon cancer that can appear in patients as young as their mid-20s as well as in older adults. Silencing of the MLH1 gene by methylation is observed in 20% of sporadic colorectal cancer. Colorectal tumors with MLH1 silencing or from patients with HNPCC demonstrate microsatellite instability. In early-onset colorectal cancer, diagnosis of HNPCC involves testing for MSI or analysis of MMR protein expression by immunohistochemistry. In very young patients, one should consider the autosomal recessive mismatch repair deficiency (MMR-D) syndrome, in which a child inherits a mutation in the same MMR gene from both parents. The clinical phenotype includes susceptibility to glioma, leukemia, lymphoma, or colorectal cancer in children and young adults (43).

Colorectal tumors in the AYA population are more often mucinous and right-sided than in older populations, consistent with the increased prevalence of HNPCC-associated tumors in this population. Between 80% and 90% of tumors from patients with HNPCC demonstrate MSI, and 90% of colorectal cancers with MSI have somatic TGFB2 mutations due to expansion of a repeat within the TGFB2 gene. Up to 30% of all human colorectal cancers have mutations in transforming growth factor- (TGF)-β signaling–related genes. Dr. Thomas Doetschman (BIO5 Institute) discussed a TGFβ1-deficient mouse model that displayed features of human colorectal cancer in that the colon cancer was associated with inflammatory lesions, occurred in the cecum and proximal colon, and developed into mucinous carcinoma (44). In a Rag2−/− (immunocompromised) background, both TGFβ1-deficient and TGFβ1-sufficient mice developed premalignant hyperplastic lesions with inflammatory infiltrates, but the lesions progressed to mucinous carcinoma in only the TGFβ-deficient mice. The TGFβ1-deficient mouse models have the potential to reveal clues regarding disease mechanisms in colorectal cancer that will contribute to a better understanding of this disease in AYA patients.

Dr. Ashley Hill (Children’s National Medical Center) cited data from the Surveillance, Epidemiology, and End Results program that suggested that colorectal cancer has a similar natural history in patients aged 15–29 years and in older patients. It has been speculated that delayed diagnosis and treatment play a role in the poorer outcomes observed among AYAs. A retrospective review of 77 pediatric colorectal cancer patients showed that the frequency of mucinous adenocarcinoma was considerably higher among children (62%) than among adults (11%–13%). Overall, 86% of patients had advanced-stage disease at presentation, with more than half exhibiting distant metastases.

Clinical symptoms of colorectal cancer in children mirror those found in adults and include abdominal pain, weight loss, and anemia, but the rarity of colorectal cancer in children compared with other causes of abdominal discomfort often prolongs the interval from onset of symptoms to diagnosis. In this study, the length of this interval did not appear to be associated with outcome because children who presented with an acute onset of symptoms invariably had more advanced stages of disease. Although the lack of colorectal cancer screening among children and the clinical features noted may contribute to a perceived poorer outcome in children with colorectal cancer, the markedly higher incidence of mucinous and signet ring adenocarcinoma in children suggests that there are potentially important biological differences between colorectal cancer in children and adults.

Dr. David Thomas (Peter McCallum Cancer Center) and Dr. Archie Bleyer (Oregon Health and Sciences University) discussed the published data that have suggested that patients with early-onset colorectal cancer are more likely than older patients to present with advanced-stage disease, to have mucinous tumors, to have poorly differentiated and right-sided cancers, and to have a higher proportion of rectal cancers. For patients younger than 30 years, the literature strongly suggests an overall survival disadvantage. However, it is not clear whether patients younger than 45 years have worse outcomes than their older counterparts when stage of disease is taken into account. There may be stage-independent and age-related outcomes in patients younger than 30 years, suggesting that there may be biological differences in cancers that affect the very young. Such biological differences may be associated with inherited predisposing syndromes or with other risk factors, such as inflammatory bowel disease, whose incidence is greater in younger populations.

Dr. Michael LaQuaglia (Memorial Sloan-Kettering Cancer Center) pointed out that there are few reports of colorectal cancer in patients aged 30 years and younger, and most that do exist are case histories or small institutional series. To address this deficit, a retrospective multi-institutional review was conducted using a total of 167 patients aged 10–30 years (median age = 21 years) who were identified through a survey of COG institutions; of these patients, 40% had a family history of colorectal cancer. Tumors were relatively evenly distributed throughout the colon and rectum. Most of the patients presented with stage III or IV disease, and 60% had distant metastases. Very few of these tumors were well differentiated, with 37% and 55% being poorly and moderately differentiated, respectively. Signet ring histology was observed in 23% of the tumors and was more commonly seen in younger patients within the cohort. MMR-D was identified via immunohistochemistry in 17% of the tumors. With a median of 48 months follow-up, median overall survival for this cohort was 44 months: 88 of 159 patients died. Compared with adult patients, a higher proportion of AYA colorectal cancer patients had stage III and IV disease and a worse overall prognosis. The proportion of tumors with signet ring cell characteristics was also higher but was not associated with a difference in survival. Within each age group, patients with MSI tumors demonstrated more favorable outcomes than those with microsatellite stable tumors. However, AYA colorectal cancer patients with either MSI or microsatellite stable tumors had worse disease-specific survival than their older counterparts. These data suggested that colorectal cancer among patients of this age group was associated with unique clinical and biological properties.

**Statistical Issues in Working with the AYA Population**

Dr. Lisa McShane (National Cancer Institute) highlighted statistical challenges in the molecular characterizations of AYA cancers
and clinical trial design. Key issues include whether AYA cancers are biologically homogeneous or reflect heterogeneous subtypes, and whether they are distinct from pediatric and adult cancers or merely reflect a shift in subtype distribution. Clinically, it will be important to identify prognostic and predictive biological subtypes that relate to disease natural history or predict patient response to certain therapies and critical to expand and coordinate specimen collections with standardized pathological and clinical data.

High-dimensional molecular profiling provides a promising approach to elucidate the biology of AYA cancers and develop informative clinical tools. Unsupervised statistical analysis methods such as clustering can be used to identify biological subgroups suggestive of therapeutic targets. A variety of supervised analysis methods are available to construct prognostic or predictive classifiers or risk scores (45, 46).

Dr McShane discussed the design of oncology clinical trials (47, 48). AYA patients may have highly variable biology independent of disease, and patient accrual to clinical studies is challenging. Phase I trials of AYA cancers should include pharmacokinetic and pharmacodynamic goals because hormonal or other biological differences may affect drug dosing and scheduling. Single-arm phase II trials may require less than half the sample size of some randomized phase II trials to achieve comparable type I (α) and type II (β) error. However, their reliance on historical benchmarks can be problematic, particularly if AYA cancers represent rare biological subtypes (49). Various randomized phase II trial designs have been proposed for rare cancers: for example, when screening trials are done for preliminary comparison of an experimental treatment to the standard regimen, the screening design allows for larger type I and II errors and targets a larger effect size than a phase III trial (50), thereby allowing smaller sample size than a typical phase III trial.

Phase III trials can be made more efficient by stratifying biological subgroups to adjust for variability or enrich for patients most likely to benefit from a new therapy. Enrichment designs provide no information for excluded patient subgroups and require a robust assay to identify the targeted subgroup, but they avoid dilution of treatment effects by patient subgroups thought unlikely to benefit from the experimental therapy. Factorial designs can test multiple treatments in combination so that patients serve “double duty” to provide information on more than one treatment, but interpretation can be complicated if treatment interaction effects are present. Systematic review and meta-analysis techniques can be used to draw conclusions across a series of studies (51) and could be fruitful if AYA data can be extracted from previous larger clinical trials.

Conclusions
For all of the AYA cancers discussed, one priority is to ensure the availability of an adequate number of tissue samples to ascertain whether there are biological differences based on age. For ALL, there has been improved clinical trial participation for AYA patients (eg, CALBG 10403), which should augment tissue collection. Furthermore, funding to investigate the molecular differences between pediatric and AYA ALL was secured from the American Recovery and Reinvestment Act as a result of the workshop. Additional studies are needed on pharmacokinetic differences and their impact on therapy and on protocol adherence by both physicians and patients. It is crucial to let AYA patients and referring physicians know the importance of treatment at cancer or academic centers that understand the value of sometimes treating AYA patients using pediatric rather than adult protocols and can provide access to clinical trials. Currently, there are no known preventive strategies for ALL.

For breast cancer, the consensus was that there is currently little evidence to prove that AYA breast cancer is biologically unique; however, there may be an enrichment of certain breast cancer subtypes among this age group and further research is needed. Despite the fact that AYA breast tumors were more aggressive and had a less favorable prognosis, there was no consensus that these tumors should be categorized as high risk based solely on AYA age group. It was agreed that we need better sources for well-annotated samples, increased awareness of the need for research among AYA women with breast cancer, and increased coordination between groups and institutions.

The evidence that AYA colorectal cancers may differ biologically from those in older populations includes poorer overall survival, higher prevalence of mucinous tumors, increased chromosome stability, and increased rate of MMR-D in AYA colorectal cancer patients. Some of this evidence is anecdotal, and the perception that survival rates for AYA patients with colon cancer are lower than those observed in older patients is not supported by existing Surveillance, Epidemiology, and End Results data. However, there may be substantial differences in biology and other features between different age groups even within the population of AYA patients with colorectal cancer. If age is a good surrogate for a unique tumor biology associated with AYA cancers, then studies of colorectal cancer in AYA patients will almost certainly illuminate alternative tumorigenic pathways and will also likely benefit patients in other age groups whose tumors exhibit similar biological features.

The niche occupied by AYA cancer patients is unique, sitting astride a somewhat nebulous dividing line between childhood cancers and the adult versions of the disease. The immediate steps required to further our understanding of AYA cancers are 1) to definitively determine whether there are identifiable molecular features of these cancers that distinguish them from the adult and pediatric versions and 2) to elucidate whether these differences can in some way explain their clinical behavior. Only in this way will we able to develop new approaches for identifying targets for AYA cancer prognosis and treatment and reduce mortality among this age group.

References


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**Notes**
The AYA Workshop co-chairs were B. Hayes-Lattin and K. Albritton. Breakout sessions were chaired as follows; ALL, N. L. Seibel; breast cancer, D. G. Blair; and colon cancer, J. V. Tricoli.

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