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Next Steps for Adolescent and Young Adult Oncology Workshop: An Update on Progress and Recommendations for the Future

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Abstract

Each year, 70,000 adolescents and young adults (AYAs) between ages 15 and 39 years in the United States are diagnosed with cancer. In 2006, a National Cancer Institute (NCI) Progress Review Group (PRG) examined the state of science associated with cancer among AYAs. To assess the impact of the PRG and examine the current state of AYA oncology research, the NCI, with support from the LIVESTRONG Foundation, sponsored a workshop entitled "Next Steps in Adolescent and Young Adult Oncology" on September 16 and 17, 2013, in Bethesda, Maryland. This report summarizes the findings from the workshop, opportunities to leverage existing data, and suggestions for future research priorities. Multidisciplinary teams that include basic scientists, epidemiologists, trialists, biostatisticians, clinicians, behavioral scientists, and health services researchers will be essential for future advances for AYAs with cancer.

Keywords

adolescent; biology; cancer; cancer care; epidemiology; quality of life; young adult

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INTRODUCTION

In 2006, the National Cancer Institute (NCI), with support from the LIVESTRONG Foundation, held a Progress Review Group (PRG) to examine the state of science associated with cancer among adolescents and young adults (AYAs) who were diagnosed between ages 15 and 39 years.[1] This effort spurred almost a decade of research activity on this population. To update some of the topics raised in the PRG report and examine scientific gaps and opportunities for future research on AYA oncology (AYAO), the NCI sponsored a workshop with support from the LIVESTRONG Foundation, “Next Steps for Adolescent and Young Adult Oncology: A Scientific Update,” on September 16 and 17, 2013, in Bethesda, Maryland. More than 60 academic scientists representing diverse disciplines participated. Five distinct and independent working groups (WGs) (Epidemiology, Basic Biology, Clinical Trials, Health Services and Medical Care, and Health-Related Quality of Life [HRQOL]) reviewed available AYAO scientific evidence. Reviews emphasized evidence on AYAs recently diagnosed with acute lymphoblastic leukemia (ALL), colon and rectal cancer (CRC), breast cancer (BC), melanoma, and sarcoma, as opposed to long-term survivors, in addition to providing general information on all AYAs with cancer. During the workshop, evidence and scientific needs were discussed; and, in the following year, each WG updated their evidence and developed final reports. This review provides a synthesis of these efforts, and more detailed articles are forthcoming from each WG.

A key initial decision in the workshop was related to defining AYA age. After considerable discussions about a desire to retain comparability to previous studies and the need to continue monitoring this vulnerable population, which has no current medical home, and in light of previous perspectives,[2] attendees agreed to recommend continued use of the PRG definition for AYAs: ages 15 to 39 years at diagnosis.[1] The group also concluded that this age range should be flexibly applied, depending on specific research questions. For example, biologically based definitions may be most appropriate for etiologic epidemiology and clinical trials. Developmentally based definitions are important for psychosocial research. Targeted ages or age cutoffs for clinical care research may vary by health care delivery system. The group recommended that future AYAO studies should report and include a rationale for the ages chosen. The workshop included presentations from each WG, discussions, and a refining of summaries, including discussions of understudied areas and broad future directions needed that formed the recommended “Next Steps.” This report presents an overview of research findings, describes scientific gaps, and makes suggestions for research, data, and infrastructure needs to further advance the field of AYAO.

EPIDEMIOLOGY

Although cancer is a disease primarily affecting older adults, an estimated 69,212 AYAs ages 15 to 39 years were diagnosed with cancer in 2011.[3] This is approximately 6 times the number of cases diagnosed in children aged <15 years. The Epidemiology WG analyzed incidence and survival trends overall and for the 5 selected cancers using Surveillance, Epidemiology, and End Results (SEER) data from 2000 to 2011.[4] Mortality rates were not examined because accurate information on age of diagnosis is not identifiable from data on death.

The age-adjusted incidence rate (per 100,000) for all cancers diagnosed from 2000 to 2011 among AYAs was 67.7 overall, 52.6 for males, and 82.9 for females. Of the 5 selected cancers, the highest incidence rate (per 100,000) was reported in BC (20.8), followed by melanoma (7.2), CRC (3.4), sarcoma (2.4), and ALL (1.0). Trends in incidence rates were evaluated using the average annual percent change (AAPC). The overall incidence rate did not change much over time for AYAs (<1% per year) (Table 1). Among the 5 selected cancers, incidence rates increased for ALL and CRC ($P<.05$), with the greatest increase in females; decreased for sarcoma ($P<.05$) and among males with melanoma ($P<.05$); and remained unchanged for female BC.

To examine 5-year relative survival, we limited analyses to those diagnosed during 2000 through 2006 to allow for a full 5 years of follow-up in all patients. For all cancers, relative survival in AYAs was 81.1% overall, 76.7% for males, and 84.1% for females (Table 2). Overall and for melanoma and sarcoma, AYA survival rates were better for females than for males. AYAs had better survival rates compared with older cancer patients for all cancers combined and for CRC, ALL, melanoma, and sarcoma (Table 3). Female AYAs with BC had a 5-year relative survival that was worse than that for older women. For ALL and sarcoma, AYAs had a worse 5-year relative survival than younger patients.

Overall, cancer incidence rates among AYAs have increased somewhat over time, with decreases in melanoma and sarcoma. Participants hypothesized that the decrease in melanoma incidence may reflect outreach and education targeting AYAs. Five-year relative cancer survival for AYAs is similar to that for pediatric patients and is better than that for older adults, as previously reported.[5] These data highlight the need to address survival differences in BC, ALL, and sarcoma. Although new treatment approaches for AYA ALL are being used, the results from these studies are just now becoming available and are not reflected in these survival data.[6] These data underscore the importance of continuing to monitor trends over time of specific cancers to guide future research efforts. Workshop participants agreed that there is a need to develop research resources and platforms to continue such surveillance.

BIOLOGY

It has long been hypothesized that cancers in AYAs (compared with the same diseases in younger and older individuals) exhibit unique biologic characteristics that influence response to treatment.[1] The Biology WG examined basic biologic and translational progress for the 5 selected AYA cancers. ALL is a model in which biologic differences between leukemias that occur in AYAs and younger patients have been identified and may have therapeutic implications.

Acute Lymphoblastic Leukemia

Research on biologic and genomic factors has progressed most in ALL compared with other AYA cancers, and several large, collaborative efforts have provided necessary data. Investigators from the NCI TARGET Project in High-Risk ALL performed comprehensive genomic analyses on leukemic samples from >1300 pediatric patients with ALL (ages ≥ 10 years, including AYAs), including more than 800 high-risk ALL patients (median age, 13.5

years).[7] This group discovered pediatric ALL cases with a breakpoint cluster region-Abelson tyrosine-protein kinase 1 (BCR-ABL1)-like, or Philadelphia chromosome-like (Ph-like) gene expression signature.[8,9] Although Ph-like ALL lacks the classic Ph translocation (t[9;22] or *BCR-ABL1*), it contains 1 or more of a complex array of novel genomic mutations in genes that encode tyrosine kinase signaling pathways. Pediatric and AYA ALL cohort data suggest that the incidence of Ph-like ALL increases with age, from 10% to 13% among children, to 21% among adolescents, and to 27% among young adults ages 21 to 39 years with ALL.[10]

Data from a large cohort (from birth to 39 years) have demonstrated differences in ALL genomics and associations with event-free survival.[10] The outcomes of patients with *BCR-ABL1* and Ph-like ALL were markedly inferior to those with other ALL subtypes. IKAROS family zinc finger 1 *(IKZF1)* alterations, which are markers of a poor outcome in childhood ALL, were enriched in patients who had *BCR-ABL1* and Ph-like ALL (70% and 77%, respectively) compared with those who had non-Ph-like ALL (26%) and were correlated with inferior 5-year event-free survival in AYAs. Different genetic abnormalities were observed in children versus AYAs with Ph-like ALL, and there was a higher frequency of fusions involving *ABL* class genes *(ABL1, ABL2,* colonystimulating factor 1 [*CSF1R*], and platelet-derived growth factor receptor, *β* polypeptide *[PDGFRB])* in children and a higher frequency of Janus kinase 2 *(JAK2)* translocations in AYA patients. Taken together, the kinase-activating *BCR-ABL1* and Ph-like subtypes confer a poor prognosis and make up approximately 60% of AYA and young adult ALL patients.[10] By identifying these patients at diagnosis, there is an opportunity to incorporate tyrosine kinase inhibitor treatment into current chemotherapeutic regimens to improve treatment outcomes. Plans are underway to test tyrosine kinase inhibitors in clinical trials in AYA and adult patients with ALL through the NCI National Clinical Trials Network (NCTN).

Colon and Rectum Cancer

Evidence suggests that AYA patients with CRC exhibit a more aggressive disease phenotype than adults with CRC.[11] AYA CRC exhibits a greater frequency of mucinous histology, signet ring cells, high microsatellite instability, and a higher incidence of mutations in mismatch-repair genes.[12] Relatively few molecular genetic studies have been conducted in AYA CRC.[13] The Cancer Genome Atlas has provided recent data on genes that are frequently mutated and are expressed at elevated levels in adult CRC, including insulin-like growth factor 2 *(IGF-2)*.[14] Consensus gene sets that exhibit mutations in adult CRC also have been identified.[15] These data provide a baseline for pathway analysis that could direct investigators toward novel signaling pathways in AYA CRC tumors. Even in the absence of a hereditary component, molecular targets need to be identified to enhance precision medicine approaches to AYA CRC and refine the delivery of molecularly targeted therapies.

Breast Cancer

BC is the most frequent form of cancer among women in this age group throughout the world.[11,16] In recent years, BC incidence with distant involvement, which is associated with a poorer prognosis, has had a statistically significant increase.[17] Age of onset is an independent risk factor, and cumulative evidence suggests that AYA BC exhibits differences

in type, grade, and aggressiveness compared with the disease in older women.[11] However, the hypothesis that this is caused by a unique biology has been debated.[18] Compared with other breast tumor subtypes, those identified in AYAs are more frequently larger, of higher grade, and more likely to exhibit a triple-negative subtype, which is generally more aggressive and has a poorer prognosis.[19] Ongoing studies have focused on specific genes, such as breast cancer 1 *(BRCA1)* and tumor protein 53 (p53), which have been linked to the early incidence of aggressive BC, and on the role of apparent difference in tumorassociated stroma.[20,21] Detailed studies of triple-negative and basal-like subgroups are particularly relevant, because they are more prevalent in AYAs.[22] No specific molecular targets are known at this time; and, although few studies of AYA BC therapeutic responses have been conducted,[23] several current clinical trials are addressing clinical issues in AYAs or comparing their cancers with those in older populations (see clinicaltrials.gov, accessed December 23, 2015).

Melanoma

The etiology of melanoma in the AYA population is not clear, but melanomas may result from the interaction of genetic and/or environmental factors and involve excessive ultraviolet light exposure among susceptible individuals. Melanomas appear to be thicker in patients aged <21 years, and those with metastases to sentinel lymph nodes (SLN) are identified more frequently in children and AYAs than in adults with the same disease stage.[24] A high mitotic rate and younger age are considered to be predictors of SLN positivity.[24] Melanoma development has been linked to germline mutations in genes encoding cyclin-dependent kinase inhibitor 2A *(CDKN2A),* cyclin-dependent kinase 4 *(CDK4),* and melanocortin 1 receptor *(MCIR)* and has been implicated in somatic mutations in proto-oncogenes v-Raf murine sarcoma viral oncogene homolog B *(BRAF), (NRAS),* and v-kit Hardy-Zuckerman 4 feline sarcoma homolog *(KIT)* and tumor-suppressor genes *CDKN2A, p53,* and phosphatase and tensin homolog *(PTEN).*[25] *BRAF* gene mutations are the most frequently detected mutations (identified in 60%−80% of patients). Among patients with melanoma ages 18 to 30 years, the *BRAF* valine to glutamic acid mutation at position 600 was identified in 38.7% of tumors and was associated with vertical growth phase and mild inflammatory infiltrate.[26] The $p16^{INK4}$ tumor suppressor gene on chromosome 9p21 is postulated as a strong candidate melanoma gene, with particular relevance to early onset familial melanoma.[27] Recent findings suggest that the differential biology of melanoma among young and older patients (age < 30 years and >60 years, respectively) is driven in part by deregulation of the microRNA (miRNA) expression that targets proliferation.[28] Several miRNA species have been identified as down-regulated or up-regulated in these different age groups. Profiles of miRNA in primary melanomas potentially are associated with the clinical parameters of disease stage and lymph node involvement that differ in adult and young populations, suggesting that different pathways of invasion are involved according to age.[28]

Sarcoma

Fusion-positive sarcomas (FPS) comprise a heterogeneous group of sarcomas (Supporting Table 1; see online supporting information).[29] Age-specific incidence of these cancers varies with diagnosis. The prognosis for AYA patients with FPS is generally poorer than that for younger patients.[11] In Ewing sarcoma, survival was inversely proportional to age and tumor

size, with worse outcomes for those aged ≥18 years older compared with those aged <18 years.[11,30] In most studies to date, survival of the tumors appears to depend on fusion genes (Supporting Table 1; see online supporting information). Treatment approaches that target these genes may improve outcome for patients with FPS. Recently, a drug-screening approach revealed that mithramycin directly inhibited the Fli-1 proto-oncogene, ETS transcription factor *(EWS-FLI1)* transcription factor.[31] A tumor-specific fusion protein is an ideal therapeutic target, because it is expressed by normal cells and appears to be required for the oncogenesis of most FPS. Unlike the commonly targeted receptor tyrosine kinases, fusion protein transcription factors have been more difficult to target. Peptides spanning the unique fusions in Ewing sarcoma and alveolar rhabdomyosarcoma have been used as part of vaccine strategies in consolidative immunotherapy, but they have not resulted in robust immune responses.[32] Alveolar soft part sarcoma is another example in which the tumor-specific alveolar soft part sarcoma chromosomal region candidate-transcription factor E3 *(ASPL-TFE-3)* fusion transcription factor is known to directly up-regulate MET proto-oncogene, receptor tyrosine kinase (MET).[33] Novel agents targeting the *MET* pathway are in clinical development and may offer a therapeutic option for patients with tumors that carry the *ASPL-TFE-3* fusion transcript.[34]

In sum, the data reviewed suggest that substantial progress has been made, but a better understanding of underlying biologic and genomic processes and their influence on disease prognosis will accelerate the development of new and more effective treatments. Workshop participants determined that specific studies, resources, and collaborations would facilitate that acceleration.

CLINICAL TRIALS

Historically, lack of participation in clinical trials was a key proposed explanation for the survival deficit of AYAs with cancer.[1] AYA participation in cancer clinical trials is reportedly the lowest of any age group.[35,36] However, accurately measuring AYA trial participation is challenging because of the variable availability of disease-specific studies and because there is no standard method for capturing such information.[37] Another challenge is the limited accessibility of trials in the community settings in which this population tends to be treated. In addition, the absence of a registry of newly diagnosed AYAs means that tracking the proportion enrolling in clinical trials is difficult.[38] To gauge participation in clinical trials, the Clinical Trials WG undertook an effort to examine the number of newly diagnosed AYAO patients among all patients with a specific diagnosis who were enrolled in NCI-sponsored cooperative group trials. In total, 116,665 patients of all ages with 18 invasive cancer types were enrolled between 2000 and 2010 onto 294 NCI-sponsored clinical trials, and 12,392 of those participants were AYAs. The highest AYA enrollment was among those ages 15 to 19 years, which exceeded SEER incidence rates for Hodgkin lymphoma, bone tumors, ALL, acute myelogenous leukemia, and central nervous system tumors. For those ages 20 to 39 years, clinical trial accrual exceeded SEER incidence rates for acute myelogenous leukemia, BC, and colon cancer. These figures suggest that AYAO cancer trial enrollment exceeded the population-based incidence for several diagnoses, a finding that was encouraging given the historic challenges of AYA enrollment and the common perception that insufficient trials are available for this age group. A

comparison of accrual from the NCI Community Clinical Oncology Program institutions with that from the academic centers demonstrated that 10% of participants ages 15 to 19 years and 17% of those ages 20 to 39 years came from the community.[39]

Barriers to Enrollment and Strategies to Overcome Them

The location and subspecialty of the oncologist who first evaluates newly diagnosed AYA patients may play a significant role in clinical trial enrollment. AYA patients are more likely to be entered on clinical trials if they are treated in pediatric hospitals under the care of a pediatric oncologist.[40,41] A large proportion of AYAs with cancer are treated in the community setting,[42] and AYA patients with brain tumors treated in the community setting have lower survival compared with those referred to an NCI-designated comprehensive cancer center.[43] Reasons for nonreferral by community oncologists remain speculative and in need of more research but are thought to include general nonparticipation in NCI-funded trials, lack of awareness of poor AYA outcomes, comfort level using adult regimens, and geographic inconvenience for patients. Opportunities to increase trial participation in community settings are needed. Why AYA enrollment is low even within academic centers also needs further study.[41,44]

Current mechanisms to provide AYA patients access to NCI-sponsored clinical trials are intergroup studies performed by NCI-sponsored cooperative groups through the NCTN, the Cancer Trials Support Unit (CTSU), and the NCI Community Clinical Oncology Program, which is now the NCI Community Oncology Research Program (NCORP). The first true intergroup effort to mount a clinical trial targeting the AYA population was C10403, a phase 2 study for the treatment of ALL. The study was designed to test the feasibility of delivering a pediatrictailored chemotherapy regimen to young adults outside Children's Oncology Group (COG) institutions. Having met its target accrual of 300 patients ages 16 to 39 years, C10403 represents a landmark effort in scientific collaboration among the participating NCI cooperative oncology groups and a significant step in increasing access to optimal ALL therapy for the full breadth of the AYA population.[6]

The CTSU is a service NCI provides to facilitate access to cancer treatment trials across the United State and Canada. COG studies relevant to AYAs are posted on the CTSU Website, making it easier for medical oncologists to enroll eligible patients on these trials. The first COG trial to be posted was AEWS1031, which is targeting patients with newly diagnosed localized Ewing sarcoma (clinicaltrials.gov). Additional AYA-relevant clinical trials are being developed in other cancers both by the medical oncology groups and by the COG and will be made available to all NCTN members. All trials posted by the CTSU are approved before posting by the NCI's Central Institutional Review Board, which expedites trial initiation at NCTN-participating institutions. The NCTN AYA WG is collaborating to identify other strategies for improving access to clinical trials for AYAO patients and to increase accrual through the NCTN to AYA-designated trials. The National Cancer Institute of Canada's Clinical Trials Group plans to establish an AYA Committee similar to the NCTN Working Group for the same purposes. In the United States, NCORP is designed to engage community-based physicians in NCI-sponsored clinical trials outside of the traditional academic centers and is broadening its focus to include research on cancer care

delivery and disparities.[45] This may broaden access to clinical trials for AYA patients who are treated in the community.

Despite obstacles that hinder AYA clinical trial participation, many avenues for improvement are possible. Innovative approaches to enhance AYA clinical trial participation include education and outreach efforts by advocacy organizations (eg, Critical Mass: The Young Adult Cancer Alliance). The Sarcoma Alliance for Research Through Collaboration has also broadened access to their sarcoma protocols by lowering age eligibility to those aged <18 years, as have groups in the NCTN. Mandated use of the NCI's Central Institutional Review Board with the participating NCTN institutions may facilitate cross-age enrollment of AYAs onto either pediatric or adult cooperative group trials. Barriers at the health care facility or system level may include age limits for admission or a lack of developmentally appropriate facilities; these issues are more complex and will require that pediatric and adult advocacy organizations work together. The necessary infrastructure is developing to ensure that all AYAO patients have access to clinical trials; however, outreach is still needed. The opportunity to influence trial participation through social media is tremendous. Specifically, online communities and mobile technologies could be used to raise awareness of trials and as intervention platforms. In addition, AYAO health care providers need to be educated about outcome disparities to ensure that patients are referred to centers that provide opportunities to participate on clinical trials.

HEALTH SERVICES AND MEDICAL CARE

To understand current scientific evidence and gaps related to AYAO patients' cancer care, the Health Services and Medical Care WG examined health services within 2 broad topics: care access (including location of care, time to diagnosis, insurance/financial burden) and care quality (including receipt of optimal therapies, adherence, supportive care, and AYA-specific clinical programs).

Access to Care

Little data are available to identify where AYAs are treated for cancer or the determinants of the choice of treatment center. Research suggests that outcomes for young AYAs may be better at pediatric institutions than at institutions that treat adults.[46,47] Those with cancers more common in children (eg, leukemias, sarcomas) are more often treated in pediatric hospitals, whereas those with cancers more prevalent in adults (eg, germ cell, thyroid, other carcinomas) are more often treated at adult academic centers.[46,47] Although proximity is a factor for AYAs and may impact the treatments received,[42,48,49] little is known about the choices made by young adults. It remains unclear whether the choice of treatment setting is based on factors like patient age, type of cancer, or clinic location and how these choices impact outcomes.[50]

It has long been hypothesized[1] and anecdotally reported by survivors[51] that AYAs experience delays receiving a cancer diagnosis, which may contribute to poorer outcomes than those in younger patients. However, evidence has not been uniform by cancer type or age,[52] and recent data in adolescents indicate that not all delays are associated with poor outcomes.[53] Furthermore, it is not clear which factors may drive the time to diagnosis.

Research is needed on factors such as socioeconomic disparities and insurance status, lack of a regular health care provider, and missed diagnoses or delayed referrals from primary care.

Although the financial burden of cancer care is problematic for all cancer survivors,[54] nationally representative data from the United States suggest that those diagnosed as AYAs have more lost productivity and higher annual health care expenditures than cancer survivors diagnosed at older ages.[55] More young adults (than middle-aged or older adults) report that cancer caused them Financial problems.[56] AYAs also have challenges obtaining care because of a lack of health insurance.[57] Uninsured young adult cancer patients have been more likely to present with metastatic disease and have higher all-cause mortality than insured patients.[58] Although policy changes stimulated by the Affordable Care Act have expanded insurance coverage for AYAs in the United States, with increases in coverage particularly for those aged ≤26 years,[59] substantial differences have been demonstrated for young adults ages 18 to 34 years in Medicaid expansion versus nonexpansion states.[60] The impact of these policy changes have not yet been fully realized for young adults.

Care Quality

It is challenging to determine the extent to which AYAs are receiving recommended treatment, primarily because of the lack of consensus on the definition of appropriate therapy for this population. Research has indicated that AYAs receive less aggressive therapies compared with children[61] and receive more aggressive therapies compared with older adults.[62] ALL has been studied most extensively, and research indicates that pediatric-based protocols provide appropriate therapy for young adults.[63] A recent study examined the receipt of consensus-based, recommended therapies among AYA patients with ALL, lymphoma, germ cell cancer, or sarcoma and observed that 24% to 34% of the sample did not receive appropriate initial treatment.[64] Factors contributing to treatment disparities included cancer type and clinical trial enrollment. One compounding factor related to treatment is adherence. Although nonadherence has been identified as a major challenge for adolescents with chronic illness compared with children and adults,[65] data specific to AYA cancer patients are limited. Existing research suggests that AYA cancer patient compliance to oral medications is suboptimal.[66] Furthermore, AYAs report psychological challenges to adherence, such as perceived lack of control and aversion.[67] Given the deleterious impact of undertreatment, research is needed to understand patterns of cancer care delivery for AYAs, including nonadherence.

Over the past decade, several medical centers have formed AYA programs that include both medical and psychosocial care. To help guide such programs, in 2010, the LIVESTRONG Young Adult Alliance prepared a consensus-based position statement regarding critical elements of care.[68] In 2012, the National Comprehensive Cancer Network published the first set of clinical practice guidelines for supportive care for AYAO.[69] Other organizations have developed criteria for becoming an AYA Center of Excellence based on professional consensus.[70,71] These recommendations highlight the need to empirically confirm that AYA-focused programs are providing recommended quality care and to determine patient

outcomes at those centers. Results from a survey of 20 US AYA programs presented at the workshop demonstrated extensive variability in the type of care provided across programs.

In sum, data on AYA cancer care services are sparse. There is no medical “home” for AYAs with cancer, and it is not clear where they are predominantly being treated. Current AYA cancer care research suggests possible delays in diagnosis, suboptimal therapy, adherence issues, and financial challenges, with little clarity about factors related to the receipt of recommended care.

HEALTH-RELATED QUALITY OF LIFE

Although there are extensive data documenting HRQOL experiences in adult survivors of pediatric cancers,[72] HRQOL has been less well characterized in individuals diagnosed with cancer as young adults. The HRQOL WG reviewed available evidence on AYA physical, psychological, social, and spiritual/existential HRQOL domains.

Significantly worse HRQOL among AYAs with cancer has been reported both in recently diagnosed and in long-term AYA cancer survivors in 2 large cohort studies. The results indicated inferior outcomes in global HRQOL as well as physical, emotional, social, and cognitive domains compared with healthy AYAs or agematched population norms.[73,74] Young adults with BC and CRC have reported poorer physical functioning than older cancer patients,[75,76] although this observation is not consistent.[77] AYAs with cancer have more comorbid conditions, report greater levels of fatigue and sexual dysfunction, and report worse self-rated physical health compared with AYAs without cancer.[73,73,78]

Cancer has a major impact on psychosocial outcomes in AYAs. AYA survivors are 1.5 times more likely than agematched peers to report clinically relevant levels of anxiety and/or depression.[79] The prevalence of psychological distress among AYAs with cancer ranges from 6% to 41%,[80,81] with higher rates of antidepressant use in AYAO patients than in their younger counterparts.[82] Cancer has a major impact on AYA relationships and vocational functioning. AYAs with cancer are less likely to be married and are more likely to divorce than AYAs with no cancer history.[83] Although AYAs report negative and positive impacts of cancer on their personal relationships, negative impacts on the spouse/significant other are most frequent.[84] Studies of work/school transition reveal that many AYAs do not return to full-time work/school.[85] AYAs who were not attending school or working during treatment were more likely to experience distress or posttraumatic stress.[81] AYA patients who reported impairments in social functioning or school/work functioning were more likely to report specific unmet service needs, and those with unmet needs reported higher symptom burden and lower quality of care.[86] However, AYAs attempt to make meaning and identify positive aspects of their cancer experience; greater religious/spiritual well being has been reported in recently diagnosed AYAs compared with AYAs who are further from the time of diagnosis.[87]

Overall, AYAO HRQOL research suffers from few comparisons with older/younger patients with cancer and with AYAs without cancer. It is difficult to determine whether outcomes are unique to age or cancer experience. Another challenge in understanding HRQOL among AYAs with cancer is the relative lack of measures developed or validated in this population.

General HRQOL instruments have been used (eg, the Medical Outcomes Study 36-item Short Form [SF-36] and the European Organization for Research and Treatment of Cancer [EORTC] Core-30 Quality-Of-Life Questionnaire [QLQ-C30]) but may be limited in assessing specific AYAO experiences. Qualitative research highlights the need for tools measuring domains, such as health behaviors, sexual and reproductive health, and support.[88] The most comprehensive validated and reliable measures developed for AYAs are the Pediatric Quality-of-Life (PedsQL) Generic Core and Well Being Scales,[89] for which there are cancer-specific modules for ages 13 to 18 years and 18 to 25 years.[90] Modified forms have been validated in AYAs with hematologic disorders.[91] Other AYA HRQOL measures include the Minneapolis-Manchester questionnaire for adolescents ages 13 to 20 years.[92] Cancer-specific HRQOL measures for AYAs have recently been developed,[93,94] and their use over time may provide a more comprehensive picture. The Patient Reported Outcomes Measurement Information System® (PROMIS®) is being validated in young adults with cancer.[95] Transitions between pediatric and adult item banks are being developed, although it is not clear how well they will capture specific experiences of AYAs with cancer.

CONCLUSIONS

AYAO research since the PRG has been prolific. All WGs noted that more research by cáncer type and age group is needed. Although AYAs are generally doing well relative to older and younger cancer patients, increases in rates of ALL and CRC must be monitored and understood. Similarly, survival disparities identified for AYAs with ALL, BC, and sarcoma suggest the need for studies to determine how nonmodifiable factors (eg, potential biologic and genomic differences) can be overcome or circumvented (eg, host-based therapies, exploitation of actionable mutations, preventive interventions) and how modifiable factors (eg, access to trials, receipt of optimal therapy) can be implemented. Finally, to best support AYAs with cancer, additional research on the best approaches to understanding and addressing symptoms and HRQOL are needed.

Access to AYA samples for studies is a challenge. One of the most important contributions to AYAO research would be pooling of data resources across institutions to include biologic samples and access to individuals during and after treatment. In the era of precision medicine, this will be imperative for advances in AYAO. The efforts and connections made during this workshop highlight the need for coordinated approaches to AYAO research in the future.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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BOX 1.

Epidemiology Next Steps

1. Examine incidence and survival trends of AYAs with cancer in general and in individual cancer types and by sex, age, race/ethnicity, and other subgroups when sample size allows.
2. Develop data resources to examine AYA cancer population trends (eg, National Cancer Database from the American College of Surgeons).
3. Develop data resources to examine treatment patterns in AYAs with cancer.

BOX 2.

Biology Next Step

1. Basic biologic and translational research studies are needed to elucidate fundamental differences between AYA cancers and the same cancer types in other age groups and ultimately to facilitate the identification of novel therapeutic targets.
2. Identify or develop AYA tissue resources with controls and annotated data and that can be made available for investigators with interest in AYA cancers.
3. Collaboration and data sharing are needed to develop sufficiently large biospecimen repositories to permit biologic and genomic studies of AYAs with specific cancer types.

BOX 3.

Clinical Trials Next Steps

1. Develop national-level mechanisms for capturing the total number of AYA patients diagnosed with cancer as well as those enrolled onto clinical trials.
2. Foster increased AYA enrollment in community practice settings (eg, within each NCTN group, the AYA and NCORP committees could work collaboratively to identify accrual opportunities, barriers, and potential solutions that could be implemented among pediatric and medical oncologists at NCORP sites).
3. Ensure that age-eligibility criteria include AYA patients in biologically appropriate, existing clinical trials, which will increase trial availability for AYA patients.
4. Increase scientific collaboration across COG and NCTN groups for future trial development in common AYA cancers. Examples of diseases to target are ALL (to build on the C10403 experience and distinctive biology and therapeutic implications in AYA patients), soft tissue sarcomas, germ cell tumors, translocation-positive renal cell carcinoma, and Hodgkin lymphoma.
5. Increase participation of newly diagnosed AYA patients in clinical trials by making the informed consent process more developmentally appropriate, educating community oncologists and other health professional about AYA disparities (eg, through the American Society of Clinical Oncology Focus Under Forty Program), and leveraging social media to raise awareness of clinical trials.

BOX 4.

Health Services and Medical Care Next Steps

1. Determine where AYAs are treated by age and cancer site (eg, pediatric hospitals vs adult-focused centers, comprehensive cancer centers, academic centers, community centers).
2. Develop studies to better examine “delays in diagnosis” (eg, data linking medical centers/health organizations with information about patient symptoms before and after diagnosis).
3. Identify data sources to evaluate the financial burden on patients and cost to the health care system.
4. Determine components and receipt of optimal cancer-directed therapy by age and cancer site.
5. Support research on patient adherence to treatments (by age, cancer site, and disease severity) and its impact on outcomes.
6. Examine the impact of expanded access to health insurance (eg, the Affordable Care Act).

BOX 5.

Health-Related Quality of Life: Next Steps

1. Well designed, prospective, controlled studies of HRQOL among AYAs are needed to examine outcomes in specific cancer types and across the survivorship continuum (including end of life).
2. Studies comparing AYAs with older and young cancer patients and survivors are needed to better determine and address unique symptom and HRQOL outcomes in AYAs.
3. Supportive-care intervention studies are needed to address physical, psychological, and social health deficits among AYAs with cancer and to improve back to school/back to work transitions.
4. Valid, reliable, developmentally relevant, and psychometrically robust measures of HRQOL, overall and by subdomain, are needed that cross the age spectrum and allow for studies of the full AYA age range.

TABLE 1.

Surveillance, Epidemiology, and End Results 18 Registries Incidence Trends for the Top 5 Cancers in Adolescents and Young Adults by Sex, 2000 to 2011

	Average Annual Percent Change		
Cancer Site	**All**	**Males**	**Females**
All invasive cancers combined[a]	0.7[b]	0.2[b]	0.9[b]
Female breast	—	—	0.1
CRC	1.9	1.4[b]	2.4
ALL	0.9[b]	0.5[b]	1.5[b]
Melanoma	−0.9[b]	−1.3	−0.6
Sarcoma[c]	−0.5[b]	−0.6	−0.3

Abbreviations: ALL, acute lymphoblastic leukemia; CRC, colorectal cancer.

[a]These include breast cancer, melanoma, thyroid cancer, testicular, non-Hodgkin lymphoma, uterine cervical cancer, Hodgkin lymphoma, CRC, central nervous system tumors, soft tissue sarcoma, oral cavity cancer, lung cancer, kidney cancer, uterine cancer, ovary cancer, acute myeloid leukemia, stomach cancer, bladder cancer, ALL, and bone sarcomas.

[b]The average annual percent change is significant ($P<.05$).

[c]Sarcomas include those of the bone, soft tissue, and joint.

TABLE 2.

Five-Year Relative Survival of Adolescents and Young Adults With Cancer and Selected Cancers Diagnosed Between 2000 and 2006 by Sex: Surveillance, Epidemiology, and End Results 18 Registries

	All			Males			Females		
Variable	**No.**	**Relative Survival, %**	**95% CI**	**No.**	**Relative Survival, %**	**95% CI**	**No.**	**Relative Survival, %**	**95% CI**
All invasive cancers combined[a]	126,308	81.1	80.9–81.3	50,714	76.7[b]	76.3–77	75,794	84.1	83.8–84.4
Survival rate > 80%									
Melanoma	14,023	94.9	94.5–95.3	5373	91.6[b]	90.8–92.4	8650	97	96.6–97.4
Female breast	18,866	84	83.4–84.5	—	—	—	18,866	84	83.4–84.5
Survival rate 50%–80%									
Sarcoma[c]	4678	69.3	67.9–70.6	2647	64.9[b]	63–66.7	2031	75	73–76.8
CRC	5997	65.9	64.7–67.2	3195	64.3	62.6–66	2802	67.8	66–69.5
ALL	1816	50.3	47.9–52.6	1192	50.1	47.2–52.9	624	50.7	46.7–54.6

Abbreviations: ALL, acute lymphoblastic leukemia; CI, confidence interval; CRC, colorectal cancer.

[a]These include breast cancer, melanoma, thyroid cancer, testicular cancer, non-Hodgkin lymphoma, uterine cervical cancer, Hodgkin lymphoma, CRC, central nervous system tumors, soft tissue sarcoma, oral cavity cancer, lung cancer, kidney cancer, uterus cancer, ovary cancer, acute myeloid leukemia, stomach cancer, bladder cancer, ALL, and bone sarcomas.

[b]The comparison between males and females was significant (P<.05).

[c]Sarcomas include those of the bone, soft tissue, and joint.

TABLE 3.

Five-Year Relative Survival of Adolescents and Young Adults With Cancer and Selected Cancers Diagnosed Between 2000 and 2006 by Age Group: Surveillance, Epidemiology, and End Results 18 Registries

	Age at Diagnosis, y								
	AYAs: Ages 15–39 y			Children: Ages 0–14 y			Older Adults: Aged ≥ 40 y		
Variable	No.	Relative Survival, %	95% CI	No.	Relative Survival, %	95% CI	No.	Relative Survival, %	95% CI
All invasive cancers combined[a]	126,308	81.1	80.9–81.3	18,385	80.7	80.2–81.3	1,968,276	63.7[c]	63.6–63.7
Survival rate > 80%									
Melanoma	14,023	94.9	94.5–95.3	246	96.7	93.3–98.4	71,274	90.1[c]	89.8–90.5
Female breast	18,866	84	83.4–84.5		—	—	295,315	89.2[c]	89.1–89.4
Survival rate 50%–80%									
Sarcoma[b]	4678	69.3	67.9–70.6	2060	74.2[c]	72.2–76.1	12,061	63.9[c]	62.9–64.9
CRC	5997	65.9	64.7–67.2		—	—	211,932	64[c]	63.7–64.2
ALL	1816	50.3	47.9–52.6	4763	88.1[c]	87.2–89	1930	19.4[c]	17.6–21.3

Abbreviations: ALL, acute lymphoblastic leukemia; AYAs, adolescents and young adults; CI, confidence interval; CRC, colorectal carcinoma.

[a]These include breast cancer, melanoma, thyroid cancer, testicular cancer, non-Hodgkin lymphoma, uterine cervical cancer, Hodgkin lymphoma, CRC, central nervous system tumors, soft tissue sarcoma, oral cavity cancer, lung cancer, kidney cancer, uterus cancer, ovary cancer, acute myeloid leukemia, stomach cancer, bladder cancer, ALL, and bone sarcomas.

[b]Sarcomas include those of the bone, soft tissue, and joint.

[c]$P<.05$ compared with AYAs.