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THE CHANGING LANDSCAPE FOR INCLUSION OF ADOLESCENTS AND YOUNG ADULTS IN CANCER CLINICAL TRIALS

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Abstract

Objectives—To discuss recent and current initiatives to increase enrollment of adolescents and young adult (AYA) cancer patients onto National Cancer Institute (NCI)-funded clinical trials in order to improve outcomes

Data Sources—Peer-reviewed publications, websites of professional organizations

Conclusion—Despite many challenges facing AYAs, recent studies illustrate that AYA-focused cancer clinical trials can be successfully developed and conducted. Development of the NCI National Clinical Trials Network and related AYA-focused initiatives create new opportunities to expand clinical trials that serve AYAs.

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Implications for Nursing Practice—Nurses can influence AYA outcomes by leveraging their roles as educators and collaborators to increase participation in cancer clinical trials.

Keywords

Adolescent and young adult; AYA; cancer; clinical trials

Cancer occurring in adolescents and young adults (AYA, defined by the United States National Cancer Institute [NCI] as 15-39 years of age),¹ is most often lymphoma, leukemia, central nervous system tumor, melanoma, thyroid cancer, germ cell tumor, or bone or soft tissue sarcoma.² However, this age group is also remarkable for its susceptibility to malignancies more commonly seen in younger or older patients, such as neuroblastoma³ and breast cancer.⁴ This spectrum of diseases, spanning as it does the age limits delineating the disciplines of pediatric and medical oncology, as well as age-specific differences in tumor biology observed for some common AYA cancers,⁵ poses unique challenges for the treatment and study of cancer and cancer-related issues in this population.

Over a period of nearly 30 years, consistently lower average annual improvement in 5-year survival has been documented for AYAs compared with younger and older age groups.⁶ The explanation for these disparities is thought to be multifactorial. In addition to poorer tolerance of intensive therapy,⁷ lower levels of treatment adherence,⁸ difficult geographical access to optimal therapy,⁹ and lack of insurance,⁹ the markedly inferior participation of AYAs in clinical oncology trials is suspected to be one of the most important factors contributing to the lower survival improvement.^{10,11} Although a causal relationship between low clinical enrollment and poorer survival improvement in AYAs is difficult to prove, their correlation is strong.¹¹ Further, survival improvements have been demonstrated when AYA patients with common pediatric malignancies are treated on clinical trials or regimens based upon recent clinical trials.¹²⁻¹⁶ In addition to improving population-level survival over time, other probable benefits of consistent enrollment of AYAs onto therapeutic clinical oncology trials include having access to novel therapies, accessioning tumor and host biospecimens, and gaining access to studies of supportive care, quality of life, and other non-survival endpoints. The importance of large-scale clinical trials as a mechanism for advancing cancer treatment has recently been affirmed.¹⁷

For all these reasons, improving accrual of AYA cancer patients onto clinical trials has emerged as a priority within the NCI-sponsored clinical trials enterprise.^{18,19} The purpose of this article is to describe new mechanisms, recent initiatives, and continuing challenges in the effort to increase participation in NCI-funded clinical trials and improve outcomes for AYAs with cancer. Table 1 provides a list of acronyms used in adolescent and young adult clinical trials.

THE AYA POPULATION IN COOPERATIVE GROUP TRIALS: HISTORICAL PERSPECTIVE

The Children's Oncology Group (COG) is the world's largest pediatric cancer consortium and was formed in 2000 through merging four separate, smaller cooperative groups

(Pediatric Oncology Group, Children's Cancer Group, National Wilms Tumor Study Group, and Intergroup Rhabdomyosarcoma Study Group). As many as 90% of the approximately 13,500 children and adolescents newly diagnosed with cancer in the United States each year are treated at COG member institutions.^{11,20} It is estimated that up to 70% of newly diagnosed children with cancer are enrolled onto clinical trials when available.²¹ Over the past 50 years, the successful conduct of sequential studies by the COG and its legacy groups, made possible in part by this consistently high level of enrollment, is considered the most important factor in achieving the current combined survival of over 80% for childhood cancer.²⁰

However, differences in enrollment exist by age. In a population-based study of data from the Surveillance, Epidemiology, and End Results (SEER) Program and COG over the time interval 1992-1997, registration of newly diagnosed patients with COG was highest for children < 5 years of age, between 5 and 9 years, and between 10 and 14 years (74%, 73%, and 63%, respectively).²¹ In contrast, registration was only 24% for patients 15-19 years of age. In a more recent analysis of patients diagnosed with cancer in the United States from 1997-2003, enrollment onto clinical trials was estimated to have occurred for only 10-15% and < 2% for patients 15-19 and 20-30 years of age, respectively.¹¹ In order to understand these differences and develop corrective strategies, it is important to consider contributing factors.

Clinical trial design is largely dependent upon the sponsoring cooperative oncology group. Protocols developed through the COG and its legacy groups historically restricted age eligibility to 21 years of age. More recent COG protocols have increased the upper age limit to 30, 40, or even 50 years in an effort to enroll more AYA patients. However, recent enrollment statistics suggest this modification alone may not be enough.^{13,22} There are many proposed reasons for continued poor enrollment. Many COG institutions are free-standing pediatric hospitals that enforce strict upper age limits (typically under 18-21 years of age) for hospital admissions and outpatient visits. Therefore, AYA patients with pediatric malignancies may need to be treated at adult hospitals having limited access to COG trials and pediatric oncology expertise. Unlike pediatric oncologists, many medical oncologists are community-based, with less direct access to clinical trials and a lower likelihood of referring an AYA patient to an institution affiliated with a cooperative oncology group.¹⁰

Conversely, lower age limits for cancer clinical trials sponsored by adult cooperative groups are typically 18 or 21 years of age, which excludes most adolescents. Even when the age limit has been lowered to 16 years, the number of adolescents and young adults enrolled on these studies is relatively low compared with older adults.²³

Historically, there has been only sporadic collaboration between pediatric and adult cooperative groups in clinical trial design. Outside of making age limits more inclusive, development of disease-specific protocols with combined input from pediatric and adult oncology investigators has been accomplished only recently.

In addition to lower AYA enrollment onto clinical trials caused by these obstacles, additional consequences are limited banked tumor specimens for basic science and translational

research²⁴ and missed opportunities for incorporation of AYA-focused secondary and exploratory aims during protocol development.

THE NCI NATIONAL CLINICAL TRIALS NETWORK

Historically, NCI-funded clinical trials were conducted through the Clinical Trials Cooperative Group Program that was established in the 1950s. Most recently, this consisted of 10 independent cooperative groups (9 adult and 1 pediatric), each responsible for its own operation and statistical center, tumor bank, and scientific support services. Based on recommendations stemming from an in-depth consensus study conducted by the Institute of Medicine, a transformative restructuring of the NCI-funded clinical trials enterprise was undertaken¹⁷ that resulted in development of the current NCI National Clinical Trials Network (NCTN),²⁵ launched in March 2014 (Figure 1). As part of this restructuring, the previous adult cooperative groups have been merged into four groups (NRG Oncology,²⁶ SWOG,²⁷ Alliance,²⁸ and ECOG-ACRIN²⁹). An additional adult group is the Canadian NCIC Clinical Trials Group. The sole pediatric group is the COG. Importantly, community-based sites that conduct NCI-funded trials, formerly known as Community Clinical Oncology Program (CCOP) institutions, interface with the NCTN through the new NCI Community Oncology Research Program (NCORP).³⁰

Although formation of the NCTN largely represents a response to declining funding, inefficient processes, complex regulatory oversight, and inadequate resources, it has created important opportunities that may benefit AYA oncology research. One of these is increased enrollment of AYAs onto NCTN clinical trials. It is hoped this will be facilitated by the NCTN platform, which is designed to facilitate cross-group enrollment of new patients onto appropriate clinical trials (eg a 25-year-old patient with Ewing sarcoma at a SWOG institution could be cross-enrolled onto the current COG study for Ewing sarcoma in patients < 50 years of age, AEW51031).³¹ A trial opened by one adult cooperative group is available to all NCTN adult cooperative groups. For a trial to allow enrollments at both COG and adult cooperative group sites, however, during trial development a COG-sponsored trial must receive NCI approval for NCTN activation or, conversely, an adult group-sponsored trial must be approved for activation within the COG. Ideally, this is accomplished by the COG and an adult cooperative group jointly developing and sponsoring the trial. Another benefit for AYAs is the NCTN requirement that participating institutions utilize the Central Institutional Review Board (CIRB),³² which provides IRB approval for both pediatric and adult institutions wishing to utilize a clinical trial. Another opportunity afforded by the NCTN is co-development of AYA-focused, intergroup clinical trials by COG and adult NCTN groups since these will realize NCTN goals of scientific integration and resource efficiency.

AYA INITIATIVES WITHIN THE NATIONAL CLINICAL TRIALS NETWORK

Prior to the development of the NCTN, individual cooperative groups had begun to form committees or working groups focused on AYA issues. Under the leadership of Dr. Archie Bleyer, in 2002 the COG became the first North American cooperative oncology group to form an AYA committee. Since 2009, the mission of the COG AYA Oncology Discipline

Committee has been to improve survival and quality of life for AYAs through a greater understanding of differences in cancer and host biology and of their adjustment to the cancer experience. Its approach has primarily been to identify gaps in AYA-focused research that are addressable in the cooperative group setting and to leverage the expertise of COG disease-specific and other scientific committees in addressing them. Progress of the COG AYA Committee and its research plan were the subject of a recent review.¹⁸ In 2013 SWOG approved creation of a formal AYA committee, and similar AYA-focused working groups are in various stages of development in the other NCTN groups.

Realizing the potential for the NCTN to facilitate AYA oncology research at national and international levels, an NCTN AYA Oncology Working Group has been formed that includes representatives from each of the NCTN groups, the NCORP sites, and NCI. The inaugural meeting of this Working Group was held in November 2013, when for the first time in history the NCI-funded cooperative groups convened to address the issue of AYA oncology. The overall goal of this Working Group is to facilitate advancement of AYA oncology research in the NCTN by establishing a means for regular, ongoing, AYA-focused interactions of all NCTN groups and stakeholders. A high priority for this Working Group is increasing the enrollment proportion of AYAs onto NCTN trials because such accrual is a *sine qua non* for any basic, translational, or clinical research linked to NCTN. Although this Working Group is still relatively new and in the process of defining its role, specific objectives have emerged that include identifying gaps where new clinical trials are needed for AYA-relevant cancers, monitoring and developing targeted interventions to improve AYA accrual across the NCTN, supporting efforts to harmonize differences in pediatric and medical oncology supportive care guidelines that are included in protocols for AYA-focused trials, and collaborating with the NCI to support efficient and effective review of proposals for AYA-focused trials. Details from the initial meeting of the NCTN AYA Oncology Working Group in November 2013 are summarized in Table 2.

RECENT AYA-FOCUSED INTERGROUP CLINICAL TRIAL INITIATIVES

As previously discussed, the most readily available tactic for increasing enrollment of AYAs on NCTN trials is expanding age-related eligibility. However, it is recognized by the NCTN AYA Oncology Working Group and the NCTN groups that the ultimate goal in collaborating should be co-development of scientifically integrated intergroup studies of AYA cancers, for which both pediatric and medical oncology expertise are needed. Such intergroup collaborations are complex processes that require time to be established in multiple disease areas, yet progress is being made. Three examples will be discussed here.

The first example is C10403,³³ a landmark study that represents the first intergroup effort focused on AYA patients. Sponsored by the Alliance (formerly, the Cancer and Leukemia Group B), ECOG, and SWOG, C10403 was a phase II prospective feasibility and safety trial for treatment of AYAs age 16-39 years with newly diagnosed B or T-cell acute lymphoblastic leukemia (ALL). This study, conducted by adult cooperative groups but designed collaboratively with critical input from the COG, was based on the observation that AYAs treated for ALL demonstrated dramatically better survival using contemporaneous pediatric rather than medical oncology-based regimens, a finding first reported in North

America but since confirmed in multiple studies internationally.¹⁵ All patients on C10403 were treated with a single regimen identical to what was then considered the "standard therapy arm" from the COG study for higher-risk ALL, AALL0232.³⁴ C10403 was open from 2007-2012 and enrolled over 300 AYAs from multiple adult cancer treatment sites. Although preliminary findings suggest this patient population did experience a higher incidence of certain toxicities during induction therapy,³⁵ induction death rates and overall mortality were low and identical to what was reported for patients enrolled on AALL0232. An interim survival analysis demonstrated substantial improvement over historical outcomes.³⁶ Based on these encouraging results, the US adult cooperative groups are planning to use the C10403 backbone for their successor trial. A comparison is underway of dose intensity and treatment toxicity for vincristine, methotrexate, and PEG-asparaginase given to AYAs on C10403 vs those on the contemporaneous COG trial.

The second example is ARST1321, an intergroup study led by investigators in COG and NRG Oncology (formerly the Radiation Therapy Oncology Group, RTOG) focused on non-rhabdomyosarcoma soft tissue sarcoma (NRSTS), a challenging group of tumors that comprises approximately 4% of all childhood and 2% of all adult malignancies in the United States.³⁷⁻³⁹ ARST1321 is exploring the efficacy of a novel multi-targeted tyrosine kinase inhibitor, pazopanib, which has been found to be beneficial in children and adults with NRSTS.^{40,41} Opened in July 2014 and now enrolling patients from both pediatric and adult sites through the NCTN platform, ARST1321 represents the first time a pediatric and adult cooperative group have co-conceptualized, developed, and conducted a cancer clinical trial that spans all ages (eligibility ≥ 2 years) for a single disease. From the perspective of AYA oncology research, already the ARST1321 experience has provided valuable insights about the process of intergroup clinical trial development. Commitment to the stated goal of developing an intergroup study proved essential, and compromise was achieved through respectful communication in various aspects of study design, such as eligibility criteria, chemotherapy dosing, dose modifications for toxicity, and radiation dosing and target volumes. Importantly, ARST1321 will yield the largest sample yet of childhood, adolescent, and adult NRSTS to understand the biological similarities and differences among them and potentially identify other actionable targets for future development.

The third example is a new intergroup task force that was recently developed to define and address AYA research needs in the area of myeloid diseases. Following the inaugural meeting of the NCTN AYA Oncology Working Group, members of the COG Myeloid Diseases Committee invited members of the adult cooperative groups to join in the creation of this Intergroup AYA-AML Task Force. Participants represent each of the cooperative groups that historically coordinated myeloid disease clinical trials (COG, SWOG, Alliance, and ECOG-ACRIN). An initial conference call was held in April 2014 during which it was decided to pursue the goal of developing an intergroup trial for AYAs with AML. Recurring monthly conference calls are held to address interim objectives in pursuit of that goal. To begin with, members from each cooperative group presented recent trial results, current trial aims, and their group's risk stratification and treatment schemas. The task force then utilized published and internal data and internal datasets to characterize AML biology and outcomes for the AYA population. The task force's next objectives include utilizing AYA-specific data to define the role of treatment response (MRD testing) and to understand the toxicity and

outcomes associated with various therapeutic approaches, including hematopoietic cell transplant.

Other initiatives are underway designed to improve the availability of cancer clinical trials for AYAs. Potential intergroup trials for Hodgkin lymphoma and malignant germ cell tumor are the subject of discussion by COG and adult cooperative group investigators. Also, interesting opportunities are being explored for increasing accrual of AYAs through the network of NCORP institutions directly funded by the NCI to improve access to NCTN trials in communities. In all these, the COG AYA Oncology Discipline Committee seeks to achieve its goals through leveraging the scientific expertise that resides within COG disease-specific and similar committees, such as Cancer Control and Supportive Care, Survivorship and Outcomes, Nursing, Behavioral Sciences, Pharmacology, and Bioethics.

FUTURE CONSIDERATIONS

As the discipline of AYA oncology continues to differentiate itself within the clinical trials enterprise, scientifically integrated NCTN studies co-developed by pediatric and medical oncology investigators represent an attractive approach for improving outcomes in this population. However, at this early stage several practical challenges exist that require additional knowledge to navigate routinely. The ARST1321 experience suggests that, in undertaking development of an intergroup study, responsibilities for each NCTN group need to be delineated early in the process. Examples include identifying the lead study group, creating common registration processes, determining how study enrollment credits are allocated, agreeing where study data will be held and which group will conduct the primary analysis, and selecting members of the Data and Safety Monitoring Committee to ensure that patients of all ages have appropriate oversight.

Because greater knowledge of cancer and host biology is essential for designing more rational and effective therapy for AYAs, a priority must be establishing mechanisms for collection, storage, and curation of biospecimens. Central reviews of study data (eg imaging, pathology) should include equal representation of pediatric and adult expertise. Age-specific secondary and exploratory aims need to be prioritized during study development. Similarly, authorship designation for trial-related manuscripts should be considered and distributed fairly among the participating NCTN groups. Further, clinical trial design needs to account for age-related differences that include pharmacokinetics/pharmacodynamics, acute and long-term treatment-related toxicity, supportive care measures, required study observations, and informed consent language and mechanisms.

Finally, a multidisciplinary approach to the AYA population itself is necessary to increase participation by encountering these patients in their unique developmental stage and identifying approaches to educate, support psychosocial needs, and address barriers and facilitators of adherence. Although not all of these are traditional components of clinical trial design, they can be provided by a multidisciplinary study team comprising oncologists, nurses, social workers, psychologists, and others.

CONCLUSION

Despite the challenges, several new developments have occurred that may lead to increased participation of AYAs in cancer clinical trials and improved outcomes. In addition to conducting research to characterize more fully the disparities affecting this population, these include creation of AYA-focused committees within the cooperative oncology groups, formation of the NCTN, and development of collaborative studies and other initiatives to expand clinical trial availability and participation for AYAs. Early experience suggests that keys to supporting collaboration in developing intergroup NCTN studies for AYAs include a deep commitment to the goal, mutual respect, effective communication, and the capacity to compromise where necessary in order to achieve consensus.

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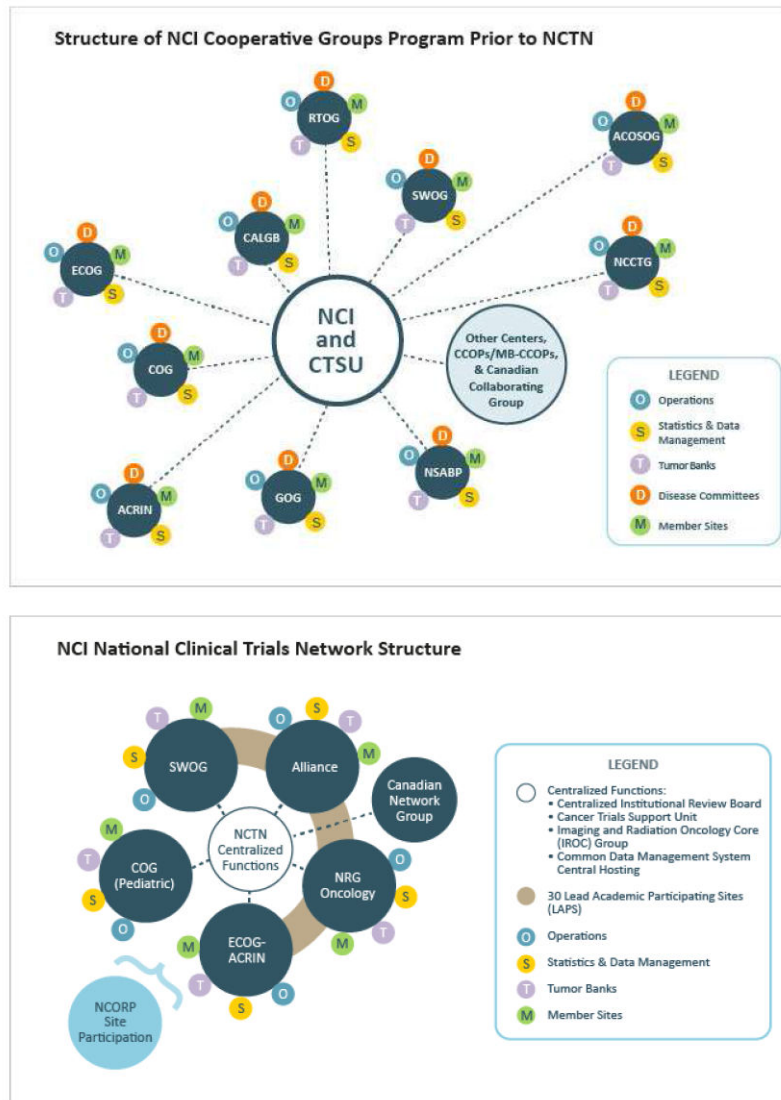


Figure 1. The NCI Cooperative Groups Program structure prior to (top) and following (bottom) the creation of the National Clinical Trials Network (NCTN).²⁵

Table 1

Acronyms used in Adolescent and Young Adult Clinical Trials

Acronym	Term
ACRIN	American College of Radiology Imaging Network
ALL	Acute Lymphoblastic Leukemia
AYA	Adolescent Young Adult
CCOP	Community Clinical Oncology Program
CIRB	Central Institutional Review Board
COG	Children's Oncology Group
ECOG	Eastern Cooperative Oncology Group
MRD	Minimal Residual Disease
NCI	National Cancer Institute
NCIC	National Cancer Institute of Canada
NCORP	NCI Community Oncology Research Program
NCTN	National Clinical Trials Network
NRG Oncology	National Surgical Adjuvant Breast & Bowel Project Radiation Therapy Oncology Group Gynecologic Oncology Group
NRSTS	Non-Rhabdomyosarcoma Soft Tissue Sarcoma
RTOG	Radiation Therapy Oncology Group
SEER	Surveillance, Epidemiology, and End Results
SWOG	Southwest Oncology Group

Table 2

Preliminary Objectives and Action Plan for the National Clinical Trials Network (NCTN) Adolescent and Young Adult (AYA) Oncology Working Group.¹

Objective	Action Plan
Enhance AYA Accrual onto NCI-Funded Clinical Trials	<ul style="list-style-type: none"> • Increase understanding and use of NCTN in enrolling AYA patients • Facilitate change of eligibility for existing trials • Promote full scientific integration between COG and adult NCTN groups in design and development of intergroup trials
Advance AYA-focused Research Within NCTN Groups	<ul style="list-style-type: none"> • Facilitate identification of intergroup partners in relevant disease areas • Review and prioritize protocols with AYA focus and inclusion • Conduct workshops on intergroup trial development for study chairs
Identify Essential Components of AYA-Focused Intergroup Trials	<ul style="list-style-type: none"> • Identify key protocol elements, including <ul style="list-style-type: none"> – Eligibility criteria – Drug dose and schedule – Management of toxicity <ul style="list-style-type: none"> ◆ Therapy modifications ◆ Supportive care guidelines • Pursue harmonization of pediatric and adult approaches <ul style="list-style-type: none"> – Organize consensus development conference – Explore creation of a tool kit to guide investigators developing new trials

¹From inaugural meeting held November 4, 2013.