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Clinical Trial Enrollment of Adolescents and Young Adults With Sarcoma

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Abstract

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More than half of all sarcomas occur in adolescents and young adults (AYAs) aged 15 to 39 years. After the publication of the AYA series in the April 1, 2016 issue of *Cancer*, several leaders in the field of sarcoma across disciplines gathered to discuss the status of sarcoma clinical research in AYAs. They determined that a focused effort to include the underrepresented and understudied AYA population in current and future sarcoma clinical trials is overdue. Trial enrichment for AYA-aged sarcoma patients will produce more meaningful results that better represent the disease's biology, epidemiology, and treatment environment. To address the current deficit, this commentary outlines changes believed to be necessary to expediently achieve an increase in the enrollment of AYAs in sarcoma clinical trials.

Keywords

adolescent; clinical trials; National Clinical Trials Network; sarcoma; young adult

Introduction

The field of adolescent and young adult (AYA) oncology first emerged more than a decade ago with the realization that improvements in outcomes for AYAs with cancer, defined as patients aged 15 to 39 years, lagged behind those for younger and older patients.[1-4] In comparison with younger patients, treatment-related toxicities are often increased and outcomes are frequently inferior in AYAs.[5-7] Accrual to clinical trials has contributed to steadily improving overall cancer survival rates, yet the rate of enrollment of AYAs into clinical trials is significantly lower than the rate for children and often even lower than enrollment rates for older adults.[8-13] One of the key recommendations of both the 2006 National Cancer Institute (NCI) AYA report and the 2014 Centers for Disease Control and Prevention working group was to expand the number of clinical trials appropriate for and available to AYAs.[1,14,15]

Sarcomas are rare cancers, and cancers in AYAs are also rare.[2] However, these 2 groups converge significantly: when age-adjusted to the standard US population, 51% of all non-aposi sarcomas occur in AYAs.[16] Although the majority o sarcomas occur in AYAs, few are enrolled in clinical trials. This can have a snowball effect such that the safety and efficacy of the therapies that we use to treat AYA patients are never definitively established. For example, consider the following:

- What is the benefit of interval-compressed chemotherapy for Ewing sarcoma in patients older than 17 years? The landmark AEWS0031 trial of 587 patients with Ewing sarcoma included only 67 patients (11%) aged 18 years or older.[17] This led to insufficient data to determine the impact of interval compression on the primary endpoint of event-free survival for patients older than 17 years. However, the available data suggest that these patients have significantly worse outcomes and, therefore, need advances in therapy.
- What is the safe and effective dose of pazopanib (or eribulin or trabectedin) for a 16-year-old with a nonrhabdomyosarcoma soft-tissue sarcoma? Frequently, no data for adolescents are included in new drug applications submitted to the US

Food and Drug Administration (FDA). Clinical trials evaluating drugs in patients younger than 18 years are often performed years after trials in adults are complete and the drugs are FDA-approved for adults. As a result, there is no safety or efficacy information for patients under the age of 18 years in product labeling at the time of approval. Adolescent patients frequently receive a drug off label once it is approved for adults, and this then impedes accrual to prospective pediatric trials evaluating these agents and further delays publication on safe and effective uses in younger patients.

- What is the benefit of adjuvant chemotherapy for stage II-III synovial sarcoma? Synovial sarcoma is one of the most common soft-tissue sarcomas in AYAs. Synovial sarcoma is driven by a well-defined translocation (t(X;18)) and has an aggressive growth pattern that distinguishes it from many other soft-tissue sarcomas. However, randomized clinical trials for this histology are usually limited to protocols that are open to all soft-tissue sarcomas, and thus results specific to AYAs are diluted by more common histologies. Such results are not easily translated to synovial sarcoma because of significant biological differences.

There is worldwide support for increasing the enrollment of AYAs in clinical trials, yet we continue to be unable to make significant progress.[18-20] The challenges to enrolling AYAs in clinical trials are well described in Smith et al's article “Next Steps for Adolescent and Young Adult Oncology Workshop: An Update on Progress and Recommendations for the Future,”[18] and they include lower enrollment if the initial evaluating oncologist is not a pediatric oncologist. The reasons for this—geographical inconvenience for patients, a lack of awareness of poor AYA outcomes, and the comfort level of the treating physician with alternative chemotherapy regimens—are not easily overcome. These multiple layers, ranging from cooperative networks and federal regulatory bodies to individual institutions, physicians, and patients, must be systematically addressed to make progress.

Historically, there was a distinct divide between trials designed and administered by the Children's Oncology Group (COG) or its precursors, which included the Pediatric Oncology Group and the Children's Cancer Group, and those run by the former “adult” cooperative groups, such as the Southwest Oncology Group (SWOG), the Eastern Cooperative Oncology Group, Cancer and Leukemia Group B, and the Radiation Therapy Oncology Group. In 2014, the NCI's National Clinical Trials Network (NCTN) transformed its structure. The new NCTN provides a mechanism through the Cancer Trials Support Unit (CTSU) for collaboration across cooperative groups so that patients at SWOG, Alliance for Clinical Trials in Oncology (Alliance), ECOG-ACRIN Cancer Research Group, or NRG Oncology sites may enroll in COG trials and vice versa. In addition, the independent nonprofit sarcoma research consortium Sarcoma Alliance for Research Through Collaboration (SARC) sponsors sarcoma-specific trials at a limited number of centers across the country; AYAs are eligible for most SARC trials. In theory, the existence of the NCTN and SARC should facilitate increased clinical trial enrollment for AYAs. An early assessment of AYA cross-enrollment in clinical trials since the introduction of the NCTN suggests that these infrastructure changes may not have had the extent of impact envisioned (Table 1). With the

exception of the unique ARST1321 trial (Pazopanib Neoadjuvant Trial in Non-Rhabdomyosarcoma Soft Tissue Sarcomas [PAZNTIS]: A Phase II/III Randomized Trial of Preoperative Chemoradiation or Preoperative Radiation Plus or Minus Pazopanib) discussed next, only 16% of all subjects enrolled in current COG sarcoma trials are older than 18 years, even though the majority of sarcomas are diagnosed after the age of 18 years. All but 2 of these adult subjects, despite the cross-enrollment option, were enrolled at COG sites.

PAZNTIS: The First Cross-Network Sarcoma Trial

In 2011, both COG and NRG Oncology (then the Radiation Therapy Oncology Group) simultaneously proposed trials to investigate the use of pazopanib (FDA-approved for metastatic sarcoma in April 2012) in the neoadjuvant setting with preoperative radiation or chemoradiation for locally advanced soft-tissue sarcomas in children and adults, respectively. When each submitted similar but separate trial concepts, the Cancer Therapy Evaluation Program approved the concept as a joint study to be developed through collaboration between 2 equal NCTN partners. ARST1321 opened to accrual in November 2014 (NCT02180867).

The PAZNTIS study committee included representatives from both networks and from the 4 major treating specialties—orthopedic oncology, radiation oncology, medical oncology, and pediatric oncology—as well as pathology, radiology, and translational research. Ultimately, the study merged the 2 initial concepts scientifically and logistically and built on the foundation of the 2 most recently completed trials in soft-tissue sarcoma from COG and the Radiation Therapy Oncology Group (ARST0332 and RTOG 0630, respectively).

As of January 2017, ARST1321 is open at 288 sites. Fifty-six percent of the enrolled subjects have come from COG institutions, whereas the remaining 44% have been enrolled through NRG Oncology and the other NCTN groups (American College of Radiology Imaging Network, Alliance, and SWOG). Forty-eight percent of the enrolled subjects are older than 18 years. Thirty-four of the 79 enrolled subjects to date (43%) are AYAs, and the majority of the currently enrolled AYAs (26 of 34) are from COG institutions. Just more than half of the AYAs older than 18 years were enrolled at COG sites (9 of 17). COG uses a central institutional review board (IRB), and thus COG sites generally opened more rapidly than sites dependent on the longer institutional IRB process; this may account for much of the difference in the initial accrual between the groups. The differences in AYA enrollment may also reflect institutional differences in the oncology team that manages the AYA sarcoma patients.

A focused effort to encourage the enrollment of AYAs in sarcoma clinical trials is overdue. The successful completion of trials for rare cancers such as sarcoma is difficult, even when they are limited to adult patients. We recognize and appreciate that overcoming the challenges to AYA sarcoma clinical trial accrual is daunting. The SARC research network includes a limited number of academic centers yet has successfully completed more than a dozen clinical trials in sarcoma, several of which included a sizeable percentage of AYAs, and this proves that the challenges are surmountable (Table 1). The small, motivated, and energetic sarcoma community may be the ideal population for targeted process improvements aimed at increasing AYA clinical trial enrollment.

Perspectives and Experiences

NCTN: NCI-Funded Adult Networks

Although NRG Oncology, SWOG, and Alliance have conducted a number of sarcoma trials for patients older than 18 years, no adult network has served as the lead protocol organization (LPO) for a sarcoma trial that included patients younger than 18 years. There are also no non-COG AYA trials for sarcoma included in the NCTN portfolio. Historically, this has been related to the active role that COG plays in clinical trials for pediatric sarcoma patients. However, since the creation of the CTSU, no significant increase in cross-enrollment (ie, from a SWOG institution to a COG trial) has occurred.

The barriers to cross-network enrollment, based on our experiences, are as follows:

- Financial. All network members are dedicated to the conduct of clinical trials and recognize that reimbursement rates do not cover their costs.[21] The costs of enrolling subjects into a trial for rare cancers such as sarcoma are even more of a financial challenge because of the lower overall expected accrual at an individual institution. The additional confounder of opening another network's protocol, with its inherent differences in time lines and procedures, adds a steep learning curve for support staff that is time-consuming and hence expensive. This could be addressed through increased incentives for enrolling AYA subjects and subjects with rare diseases into NCTN trials.
- Lack of recognition. The requirement of a single LPO, even when a concept has been developed jointly, leads to a decreased sense of ownership by the collaborating groups. The NCTN modified the biobanking process at the same time and potentially decreased a sense of ownership in the correlative science as well. New methods of assigning academic credit in cases of joint development may help to abrogate the imbalance introduced by the single LPO structure.
- IRBs. Many local IRBs and even the NCI's central IRB divide their reviews on the basis of the inclusion of patients younger than 18 years; this adds confusion and costs and slows the process of opening trials for AYAs.
- Consent. There is often confusion regarding assent requirements and the legal age of consent, which can vary from state to state. The non-COG networks require more education on how the Code of Federal Regulations (CFR) differs for the pediatric population. These differences include additional safeguards, the elimination of unnecessary procedures, the definition of scientific necessity, equitable selection, the prospect of a direct benefit/appropriate risk benefit ratio particularly in regards to placebo-controlled trials, and safety monitoring requirements.
- Our industry partners are often hesitant to extend eligibility age limits below 18 years. As the FDA and IRBs begin questioning the nonbiological age cutoff of 18 years, we have observed some increased willingness on the part of pharmaceutical companies to include patients down to the age of 15 years and, occasionally, 12 years.

NCTN: COG

The COG experience is similar to that of the other networks in that the accrual of young adults to trials remains less than would be expected on the basis of the disease epidemiology. Two committees develop and lead trials for sarcoma patients: the Bone Tumor Committee and the Soft Tissue Sarcoma Committee. Both are committed to extending the age of enrollment for COG sarcoma trials to encompass AYAs. Specifically, the Bone Tumor Committee clinical trial eligibility has been extended to the age of 50 years unless concerns about investigational agent safety prevent it. Likewise, trials for soft-tissue sarcomas have extended the age of enrollment to 40 years for rhabdomyosarcoma. Both sarcoma committees in COG have liaisons to the COG AYA committee and have published specific analyses of clinical trial results relevant to AYA patients.[3,22]

The COG experience suggests that a lack of agreement on standard chemotherapy backbones, low institutional per-patient reimbursement for NCTN protocols, and anticipated low per-site accrual are common barriers to continued limited AYA trial accrual. From the perspective of study leaders of the co-developed PAZNTIS trial, the most critical barrier has been that only 1 group can be the LPO. Although both NRG Oncology and COG had equal partnership in the development and conduct of this trial, COG ultimately has the final regulatory responsibility, and this has led to some perception that PAZNTIS is a pediatric trial. In an effort to actively address these barriers, the PAZNTIS group has led interactive webinars and meeting forums and personally reached out to the other NCTN groups.

SARC

SARC is a nonprofit consortium of academic researchers that is funded in part through an NCI Specialized Program of Research Excellence (SPORE) grant. A goal of SARC's founding leaders, who included pediatric and medical oncologists, was to develop clinical trials including the full age spectrum for the disease being studied. When there is an exciting new therapeutic approach and both disciplines are included in the development of the study, rapid accrual across the population has been achieved (Table 1). Despite this commitment and the ability to activate studies including a lower age limit of 4 years, the enrollment of patients under the age of 18 years has not consistently been robust. From the perspective of SARC, the obstacles that hamper achieving enrollment of the full spectrum of the sarcoma population include the following:

- There is separation of programs within academic institutions. Contracting, IRB, and investigational drug services are separate for adult and pediatric departments, and this results in increased costs and complexity; often, data management teams are separate as well.
- There is a lack of complete engagement and commitment between the 2 disciplines in the design and development of study protocols.
- SARC is not an NCI NCTN grantee and is, therefore, ineligible to be an LPO or to participate in CTSU cross-enrollment.

Regulatory Agencies: FDA

To increase access to relevant investigational and approved drugs for adolescent patients with cancer, the FDA's Office of Hematology and Oncology Products strongly recommends the inclusion of adolescents (aged 12-17 years) in disease or target-appropriate adult oncology clinical trials at all stages of development.[23,24] Clinical trials for sarcomas are important examples for which this approach is relevant because there are several histologies in this heterogeneous group of diseases that occur in both adult and adolescent patients.

This recommendation is in part based on data from a 2013 review from the FDA, in which the authors evaluated 92 drugs with both adolescent and adult indications. The dosing for adolescent and adult patients was equivalent in 94% of cases, and allometric scaling was useful in predicting adolescent drug clearance.[25] For later-stage clinical trials in which dosing regimens are established and toxicity profiles are known, adolescents can be enrolled in the trial simultaneously with adults. In very early-stage trials, when the biological rationale is particularly strong, adolescents may be enrolled after initial adult pharmacokinetic and toxicity data are obtained. Adolescents should be enrolled at doses that are expected to be active to ensure that the provisions of 21 CFR§50.52 (clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit) are met. Note that the FDA generally does not require that juvenile animal studies be conducted before the initiation of pediatric trials in oncology.[26] The evaluation of age-specic toxicities, such as growth derangements and fertility issues, are not usually possible in the context of early-phase trials but should be evaluated in trials enrolling patients in earlier lines of therapy.

Discussion

There are numerous barriers to the enrollment of AYAs into cancer clinical trials, but there is perhaps no greater disease area in need of enrichment for AYA enrollment than sarcoma.

The inclusion of adolescents in adult sarcoma trials is supported from an ethical perspective, especially with the increasing recognition that the age of 18 years is a legal standard and has no significant physiological relevance. IRBs are required to ensure that the provisions of 21 CFR§50.52 are met for oncology clinical trials in pediatric patients. With appropriate patient selection and informed consent, the enrollment of adolescents in adult oncology trials is justified by the nature of the disease. As the FDA and the Cancer Therapy Evaluation Program provide further encouragement, our industry partners and local IRBs will continue to develop the understanding that including patients down to the age of 12 years is both reasonable and safe in most instances. Enrolling adolescents early in development programs evaluating drugs for sarcomas can allow the inclusion of adolescents in the indication at the time of the initial FDA approval and can expedite access to new drugs for this group of patients, a population with an unmet medical need.

Most NCTN member sites do not yet have experience in cross-enrollment, but resources exist to assist research staff. Two CTSU webinars, “Access to NCTN AYA Trials (April 22, 2015)” and “How to Enroll Onto AYA Studies—A Step-by-Step Guide (June 15, 2016),” and a slide deck, “AYA Studies: Patient Enrollment, Crediting, and CIRB Review,” are

available on the CTSU Web site (https://www.ctsu.org, under Education & Resources tab, Educational Presentations and Webinars) for interested researchers to review.

Improved communication within the sarcoma clinical research community will likely result in increased AYA enrollment as well. Such communication must begin at the individual institution level and include the establishment of joint sarcoma tumor boards, the inclusion of AYA patients in all investigator-initiated single-site trials, and the enhancement of the capabilities of local IRBs such that strict age limits are less of a barrier. Once we make headway within our own institutions, we will then be much better poised to partake in cross-network trials.

Increased incentives may be necessary to address concerns about the amount of time and resources necessary to open NCTN sarcoma trials, which will inevitably have low per-site accrual because of the rare disease being studied. In addition, sarcoma studies in particular should begin to use AYA enrichment strategies within the trial design.

Finally, there are some genuine concerns regarding the different chemotherapy backbones used by pediatric and adult centers for several sarcomas. Regimens that have proven superiority within pediatric populations may result in unexpected severe toxicity in adult populations and even in older adolescents. Without mutually acceptable regimens, AYA enrollment will continue to be limited to trials investigating second- or third-line therapies.

Conclusions

The degree of cross-network collaboration for cancers that affect AYAs has improved over the past decade but remains inadequate. A focused effort to include the under-represented and understudied AYA population in current and future sarcoma clinical trials is long overdue.

We agree with and fully support the development of joint sarcoma trials and the co-enrollment of AYA subjects between the NCTN groups. To achieve this goal expediently, we recommend that the NCTN implement the following:

1. A mechanism to have multiple organizations serving as joint LPOs. If this proves insurmountable secondary to data support and other logistical considerations, then a manner by which merit is allocated across networks must be explored.
2. Increased incentives for the recruitment of AYA patients, including increased NCTN credit for the enrollment of patients aged 15 to 39 years.
3. Common registration, reservation, and enrollment procedures and timelines.
4. Active encouragement of industry, academia, and local regulatory boards to limit the use of arbitrary age cutoffs in the development, administration, and regulation of cancer clinical trials.

Between all NCTN groups and SARC, we recommend establishing a joint sarcoma working group tasked with the following:

1. Developing guidelines for preferred study designs that are acceptable to all member groups.
2. Avoiding the activation of competitive trials.
3. Establishing chemotherapy backbone regimens for newly diagnosed patients for which a consensus on acceptable expected efficacy and toxicity across age populations is reached.

Within individual sarcoma centers, we suggest the following:

1. The identification of and support for local champions to maximize opportunities for clinical trial enrollment for AYAs with sarcoma at the institutional level. These individuals must be senior, recognized professors who have the fortitude and seasoned experience to overcome obstacles within their institutions and beyond. The efforts of young investigators may augment this work by providing focused energy. Local champions will open and activate NCTN and SARC trials in both pediatric and medical oncology settings and will spearhead regional outreach aimed at encouraging the clinical trial enrollment of AYAs with sarcoma.
2. The education of local regulatory boards on the detriments of arbitrary age cutoffs in cancer clinical trials.

Trial enrichment for AYA-aged sarcoma patients will produce meaningful results that better represent the disease's epidemiology and treatment environment. The increased enrollment of AYAs in sarcoma trials across the NCTN and SARC is required to improve outcomes for this population.

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Table 1

Enrollment in All Recent Multi-Institutional Sarcoma Clinical Trials That Included Ages Above and Below 18 Years With Some or All Accrual Occurring After the Establishment of the Cancer Trials Support Unit

Trial	Disease	Participating Groups	Enrollment Period	Eligible Ages, y	Total Enrolled, No.	≤18 y, No.	>18 y, No.	Adult Enrollment (>18 y), %	Total AYAs Enrolled, No.	AYA s (15-39 y), %
AEWS1031	Ewing	COG, NRG Oncology	11/2010-1/2016	≤50	642	552	90	14	243	38
AEWS1221	Ewing	NCTN	12/2014 to ongoing	≤50	131	106	25	19	63	48
AOST1321	Osteosarcoma	NCTN	11/2015 to ongoing	≤50	37	32	5	14	29	78
AOST1322	Osteosarcoma	NCTN	8/2014-7/2015	12-50	19	15	4	21	16	84
AOST1421	Osteosarcoma	COG	11/2015 to ongoing	≤30	17	14	3	18	9	53
AOST1521	Osteosarcoma	NCTN	2/2016 to ongoing	12-50	21	7	14	67	17	81
ARST1431	Rhabdomyosarcoma	NCTN	5/2016-9/2016	≤40	11	11	0	0	0	0
PAZNTIS[a]	STS	NCTN	7/2014 to ongoing	≥2	79	31	48	61	34	43
SARC001	Multiple	SARC	11/2001-12/2005	≥10	51	7	44	86	32	63
SARC003	Multiple	SARC	5/2005-5/2009	≥4	54	3	51	94	27	50
SARC006	MPNST	SARC	9/2006-6/2012	All ages	49	3	46	94	31	63
SARC009	Multiple	SARC	5/2007-11/2010	≥13	353	5	348	99	83	24
SARC011	Multiple	SARC	12/2007-4/2010	≥12	323	72	251	78	211	65
SARC012	Osteosarcoma	SARC	6/2009-4/2014	15-74	46	12	34	74	40	87
SARC023	Multiple	SARC	6/2014-2/2015	≥16	10	1	9	90	6	60
SARC025	Ewing	SARC	6/2014-11/2016	≥13	19	3	16	84	17	89
SARC028	Multiple	SARC	2/2015-1/2016	≥12	86	7	79	92	37	43

Abbreviations: AYA, adolescent and young adult; COG, Children's Oncology Group; MPNST, malignant peripheral nerve sheath tumor; NCTN, National Clinical Trials Network; PAZNTIS, Pazopanib Neoadjuvant Trial in Non-Rhabdomyosarcoma Soft Tissue Sarcomas; SARC, Sarcoma Alliance for Research Through Collaboration (nonprofit consortium of academic clinical researchers); STS, soft-tissue sarcoma.

The data are as of September 30, 2016, except for the PAZNTIS data (January 16, 2017).

[a]PAZNTIS was jointly developed by NRG Oncology and COG; COG serves as the lead protocol organization.