Regulatory Barriers to Clinical Trial Enrollment of Adolescent and Young Adult Oncology Patients

abstract

Adolescent and young adult (AYA) patients with cancer may face unique challenges if they and their families wish to participate in clinical oncology trials. Regulatory guidelines and funding requirements put in place to protect patients may actually raise barriers to enrollment in clinical trials. Hospital age guidelines may need to be readdressed to better suit the needs of AYA patients. Finally, the creation of the National Clinical Trials Network will provide new opportunities for pediatric and medical oncologists to collaborate in the care of AYA patients. Pediatrics 2014;133:S119–S122
A treatment facility with medical oncologists for adult patients with cancer is currently managing an 18-year-old male patient newly diagnosed with osteosarcoma, a 17-year-old female patient with acute lymphoblastic leukemia (ALL) who lives 300 miles from a Children's Oncology Group (COG) institution, and a 19-year-old male patient with Wilms tumor whose adult oncologist is unfamiliar with his pediatric renal tumor. As adolescents and young adult (AYA) patients with cancer, they all share one common attribute: regulations and rules may act as barriers to prevent them from participating in clinical trials.

THE CHALLENGES

Health care professionals in both pediatric and adult oncology are becoming increasingly aware of the need to create systems that facilitate the enrollment of AYA patients with cancer into clinical trials to increase their survival rates and improve their quality of life. As professionals in both pediatric and adult oncology programs brain-storm strategies to facilitate enrollment, they encounter barriers in cultures of the medical specialties, health care finance and reimbursement, guidelines that govern the running of institutions, and regulations and funding requirements related to the conduct of clinical trials.

In an interactive interdisciplinary forum at a recent pediatric oncology meeting, participants identified the challenges they face in caring for AYA patients at their pediatric institutions. Some pediatric hospitals prohibit admissions of young adults aged >18 years; others cite 21 years of age as their upper limit, whereas others will allow admission of older patients for tumor types that are considered in the pediatric realm or if there is an open treatment protocol. In addition, pediatric oncology physicians and advanced practice providers may have personal, hospital privileging, and/or liability concerns in caring for young adult patients. Although children's hospitals may provide exceptions for admitting young adults with a pediatric type of cancer, family practice physicians and nurse practitioners in the community may be more familiar with adult cancer programs and naturally refer their patients to adult-treating oncologists. In addition, third-party payers may direct their subscribers to lower-cost community oncologists. However, to those providing care, the regulations seem the most complex of all of these difficulties to overcome.

COG is a National Cancer Institute– supported clinical trials group. It is the largest research organization devoted exclusively to pediatric and adolescent cancer research. Like all cooperative groups and cancer centers, it is subject to numerous regulations starting within its member institutions and encompassing several federal and state regulatory bodies. Although all the regulations have been put in place to protect patients and the quality of research, at times these rules are preventing patients from receiving optimal care, especially for young adults with pediatric-type malignancies.

Many of the trials open to AYA patients are administered by COG. COG and other adult cooperative groups that enroll young adults must adhere to the federal rules and guidelines regarding research as well as their own constitutional rules. At the governmental level, most rules and policies governing clinical research stem from the Office for Human Resource Protections (OHRP) and the National Cancer Institute's Cancer Therapy Evaluation Program (CTEP). OHRP provides guidelines regarding what it means to be “engaged in research.” If the site or institution providing care to a patient meets the definition of being involved in research, then all of OHRP’s human subjects rules apply to this site. Sites are considered to be engaged in research if their employees obtain for the purposes of research the following: (1) informed consent; (2) identifiable private information about subjects; or (3) data about the subjects, including drawing blood, administering drugs, or other treatment. If a site is considered to be involved in human subject research, the site must hold a Federalwide Assurance certificate that certifies the institution or site meets the standards for performing human subject research and have an institutional review board (IRB) overseeing their research. There are rare exceptions that allow the use of a nonapproved treatment center for the administration of protocol therapy in an emergency or for a short designated time (ie, patient vacation). However, recent interpretation of the guidelines by OHRP have restricted where clinical trial participants can receive their chemotherapy, even if the medication in question is not an investigational agent and is considered standard of care.

CTEP supplies an investigator handbook that provides additional guidelines for research studies. There are several specific guidelines pertinent to patients whose age may bridge both pediatric and adult oncology. First, most, but not all, protocol treatments and observations for a clinical trial must be made by the physicians affiliated with the agency running the trial (ie, COG) and be registered as an investigator with CTEP. Second, if an investigational agent is part of the protocol, patients appropriately must receive this agent at the institution where consent took place. These guidelines do allow for certain treatments to be administered under certain conditions by physicians not registered with CTEP.
COG’s current rules and regulations require that institutions and its members meet stringent criteria for membership. This condition allows COG to maintain the high level of competency required to do clinical research. COG has chosen not to have affiliate sites and follows the National Cancer Institute funding requirement that multiple sites of research must be under the same medical group and have a single IRB of record. Because the list of membership requirements includes such criteria as a PICU, it is difficult and not necessarily ideal for an adult-only hospital to become a COG institutional member. Radiation oncology is frequently given at a non-COG treatment site. For quality purposes, the site must have an investigator who is responsible for radiation therapy who is a COG member and the site qualified by the Quality Assurance Review Center, the latter being a long-established research resource for clinical investigators around the world.4

It is possible for an adult oncologist to be a member of COG and practice within a COG institution. However, cultural and geographic differences may impede this practice. AYA patients could be enrolled in a COG study by a non-COG member if that study is posted on the Clinical Trials Support Unit Web site. To date, however, only 1 study has been posted, and this program is being phased out. A study could not be posted unless endorsed by 2 separate clinic trials groups. The interest from the adult cooperative groups was low given the small volume of AYA patients they have with these pediatric diseases.

Thus, what challenges does our 18-year-old male patient with newly diagnosed osteosarcoma face? He was referred by his family physician to the adult oncology service at a private adult hospital. Across town, there is a children’s hospital that is a member of COG. The adult oncologist would like to enroll this patient in the COG trial for patients with localized osteosarcoma. The study is not available via the Clinical Trials Support Unit, and it is not available at the adult hospital because the institution would not qualify to be a COG institution. Although the patient could travel to the children’s hospital to be consented and enrolled in the clinical trial, because the adult hospital has a separate IRB and meets the OHRP and CTEP guidelines of an institution that is participating in human subject research, under most circumstances, the patient would not be able to receive the COG clinical trial chemotherapy with his oncologist at the adult center. The adult hospital’s IRB is not willing to cede regulatory supervision of the study to the children’s hospital, and the children’s hospital does not want to accept responsibility for care provided at another institution. If radiation therapy were required as part of the study, the problem is further magnified if the radiation oncology center did not have a COG-responsible investigator. The most straightforward way, and usually the only way the patient could participate in the COG clinical trial, would be a full transfer of the patient to the children’s hospital for the duration of his care.

The 17-year-old female patient with ALL is being treated at a COG institution and is eligible to enroll in the COG high-risk ALL trial. The family would likely need to be near the treating hospital for the first 9 months of therapy for patient safety reasons. However, the maintenance phase that follows for a total of 2 years of therapy requires outpatient chemotherapy with intravenous vincristine every 4 weeks. The maintenance therapy she would receive would be considered standard of care for any patient not in a clinical trial. She lives 300 miles from the nearest COG institution. For economic reasons, the family wishes to receive 2 of her 3 monthly vincristine injections closer to home. There are 2 options in a nearby town. One is a pediatrician who has occasionally administered vincristine. The other is an adult oncology outpatient unit in a larger regional hospital that participates in other clinical trials and has a CTEP site designation. However, the site does not share the same IRB as the consenting institution. Thus, despite being a CTEP-certified research site, the local institution is not, according to OHRP policy, allowed to provide the monthly doses of vincristine.

CTEP does provide an option for administering the vincristine in a private physician’s office. It must be clear that this office does not meet any of the guidelines for engaging in research. The site must cede responsibility of oversight of research to the COG hospital’s IRB who must be willing to accept this responsibility. There must then be an agreement in place to clearly define the responsibilities of both parties. COG provides clear guidelines on what protocol interventions can and cannot be performed at this hometown site. Therefore, this patient potentially could receive some of her protocol medications closer to home, but because of the OHRP regulations, she would have to receive chemotherapy at a nononcology physician’s office rather than the adult-centric, certified, cancer center. However, as the cooperative groups move to using a central IRB, it is not clear what will happen to this process.

Our third patient, the 19-year-old male patient with Wilms tumor, is too old to be admitted to the children’s hospital per local hospital rules. Many children’s hospitals have acknowledged that pediatric diseases are best treated by physicians with expertise in that disease. Some have lifted the age requirements for admission if a patient has a pediatric disease or qualifies for a pediatric protocol that is not available elsewhere. Unfortunately, this
The good news for AYA patients and their providers is that there are upcoming changes that should ease enrollment into oncology clinical trials, no matter who is providing the care. The National Cancer Institute is in the process of revamping their clinical trials system into the National Clinical Trials Network Program (NCTN). The new system will consist of COG and 4 adult cooperative clinical trials groups who have recently applied for approval and funding. As currently designed, any provider who is a member of the NCTN will have access to clinical trials in the other groups. For example, our adult oncologist, if he or she was at an institution that was part of NCTN, would be able to enroll this 18-year-old with osteosarcoma into the COG osteosarcoma clinical trial if the patient meets eligibility requirements. Conversely, COG institutions will be able to access trials in any of the adult cooperative groups for which the patient is eligible.

CONCLUSIONS AND RECOMMENDATIONS

As one of the world’s childhood cancer expert groups, COG is dedicated to working with COG member institutions and patients’ local resources to deliver the most appropriate care in the most appropriate setting. They have amended protocols to envelope AYA patients into pertinent clinical trials. However, they can continue to look for opportunities to better accommodate this age group. Their members should work with local institutions to identify appropriate admissions based on resources and outcomes, not age. COG should continue to try and implement creative problem-solving to develop a new model for caring for AYA patients outside the COG institution as was done for patients receiving radiation therapy at non-COG sites. New strategies are needed to provide access to clinical trials for the AYA population while assuring their safety.

Governmental regulations, particularly recent OHRP interpretations, need to be reviewed from the aspect of what is providing clinical trial subjects protection as opposed to what are actually obstacles for optimal care.

The new NCTN cooperative groups should each have their own AYA committee to mirror the AYA committee from COG. Collaborative work between COG’s AYA committee and the current SWOG has already begun. In the end, it will take highly motivated clinicians in both the pediatric/adolescent and adult worlds as well as representation from regulatory bodies to develop innovative solutions to address the unique needs of the AYA patient with cancer.

REFERENCES

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