Improving Enrollment in Clinical Trials for Adolescents With Cancer

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**KEY WORD**
AYA oncology

**ABBREVIATIONS**
AYA—adolescent and young adult
COG—Children’s Oncology Group
NCI—National Cancer Institute

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**abstract**

Overall cancer cure rates have risen over the last 30 years. Adolescent and young adult (AYA) oncology patients aged 15 to 39 have not shared in these successes as an age group, including those who fall into the younger age group of 15 to 19 years. The reasons for this deficit in survival improvement are manifold, but research has shown that an important factor is decreased enrollment in therapeutic clinical trials in this population versus younger patients. The paucity of adolescents treated in clinical trials is itself the result of several elements of the health care landscape in the United States. On the local level, these factors include referral patterns and facilities available; on the national level, related factors include the number of clinical trials available for this age group and health care provider education in the care of these patients. We examine the data available that have contributed to this deficit in the United States and offer broad strategies to address these shortcomings with the goal of improving outcomes in this underserved population. *Pediatrics* 2014;133:S109–S113
Cancer cure rates have improved significantly over the last 30 years; however, most of this increase has occurred among children and older adults, with little or no improvement in adolescent and young adult (AYA) oncology patients aged 15 to 39 years. The survival improvement in the pediatric population up to the age of 15 years and lack of progress in the AYA oncology patients, including the youngest of this age group (15–19 years old), can be partly attributed to enrollment and treatment in national cooperative clinical trials. It has already been well documented that both the United States and the United Kingdom have inferior clinical trial enrollment rates for adolescents compared with children aged <15 years, and there is evidence that improved cure rates correlate directly with higher rates of clinical trial participation.

The focus of the present article was the problem of clinical trial enrollment in younger AYA patients (i.e., adolescents aged 15–19 years) who fall easily into the age range targeted by pediatric cancer centers and pediatric cooperative clinical trials. Our main objective was to examine the causes of the clinical trial enrollment discrepancy in adolescents aged 15 to 19 years versus younger age groups and to describe strategies to address this issue.

**CLINICAL TRIAL ENROLLMENT RATES IN ADOLESCENTS**

The participation rate of 15- to 19-year-olds in the United States in national cancer treatment trials sponsored by the National Cancer Institute (NCI) during 1997 to 2003 was 50% of that of the corresponding rate in patients aged <15 years. Similar data at the Children’s Hospital of Pittsburgh demonstrated that clinical trial enrollment is lower in 15- to 22-year-old oncology patients compared with pediatric oncology patients aged <15 years. Of 640 new oncology patients seen over 5 years at that center, 139 patients (22%) were 15 to 22 years of age. Thirty-six percent of all patients were treated in a clinical trial, including 38% of children and 27% of the older patients. Fifty-seven percent in the older group were not enrolled because there was no open clinical trial available to them versus 41% in the younger group. The same investigators later noted an even larger disparity in clinical trial enrollment when AYA patients aged 15 to 22 years were treated at the affiliated adult oncology center, where only 4% of patients in this age range were enrolled in clinical trials. These data suggest that location of treatment at a pediatric oncology treatment facility, as opposed to an adult medical oncology treatment facility, may have an impact on whether patients are enrolled in clinical trials.

Parsons et al examined data on 1358 AYA patients with cancer (ages 15–39 years) in the Surveillance, Epidemiology, and End Results Program and found that only 14% of patients aged 15 to 39 years were enrolled in a clinical trial. Multivariate analyses demonstrated that the following patients were less likely to be enrolled in clinical trials: those who were uninsured (3% vs 14%), aged >19 years (<10% vs 34%), and not treated by pediatric oncologists (9% vs 53%).

These data allude to other important barriers to clinical trial enrollment in these patients: referral patterns and the facility where the adolescent is ultimately treated. There is significant evidence that most newly diagnosed oncology patients aged >15 years are treated in community oncology facilities and not in tertiary care centers such as a children’s hospital or an adult cancer center that participate in NCI-sponsored cooperative clinical trial groups. In a study of the pattern of treatment of AYA oncology patients in Ohio, 76% of 15-year-old oncology patients were treated at pediatric oncology centers compared with only 36% of 17-year-olds and 23% of 18-year-olds. Therefore, most of the younger AYA oncology patients (aged 15–19 years) were not seen at a center that could offer them the most clinical trials for their specific diseases, and this deficit increases with advancing age of the patient. Of >10 000 children aged <20 years with cancer who were identified by the 11 Surveillance, Epidemiology, and End Results Program registries between 1992 and 1997, only 5796 were registered with the Children’s Cancer Group or the Pediatric Oncology Group, the only cooperative pediatric cancer organizations in the United States at the time. Further analysis found that the age-adjusted registration rates were 71% for children aged <15 years and only 24% for adolescents aged 15 to 19 years. Registration with the groups is not indicative of participation in a clinical trial but rather inclusion in the database of all patients treated at that center and therefore a surrogate for access to a larger number of trials. Of note, the Children’s Cancer Group and the Pediatric Oncology Group merged in 2000 to form the Children’s Oncology Group (COG) to further advance clinical trial use in children, adolescents, and young adults with cancer in North America. Unfortunately, the centers that open the COG treatment and biology trials, some of which can enroll patients as old as 50 years, are almost exclusively children’s hospitals in North America whose upper age limit is rarely higher than 22 years.

The discrepancy in referral patterns of adolescent patients with cancer compared with pediatric patients is further detailed in Albritton and Coccia’s article in this series in *Pediatrics*. However, it is important to note that even when adolescent patients are referred to
a tertiary care center with access to cooperative oncology group trials, there still may not be a study available because there are limited available AYA trials open for enrollment at any given time. Even for acute lymphoblastic leukemia, the most common malignancy for those aged <20 years (and which has seen more progress than any other), the participation rate is strikingly less in 15- to 19-year-olds than in younger patients. An analysis of a recent report from COG confirms that AYA oncology patients aged 15 to 19 years in COG trials have had an increase in survival, as others have reported, but that their progress is lagging considerably behind younger patients. The 5-year death rate in the most recent COG cohort was 25% for 15- to 19-year-olds versus 10% for all age groups combined. For 10- to 18-year-olds enrolled in St Jude Children’s acute lymphoblastic leukemia trials, the 5-year death rate was 28.9%, 23.8%, 26.9%, and 31.2% in successive studies during 1984 to 1999.

STRATEGIES TO INCREASE ENROLLMENT IN CLINICAL TRIALS FOR 15- TO 19-YEAR-OLDS WITH CANCER

Because the shortfall in clinical trial enrollment among AYA oncology patients is the result of multiple challenges in the current health care system, multifaceted strategies should be used to correct this problem. These strategies include increasing referrals to cancer centers that offer clinical trials, establishing joint pediatric/medical AYA oncology programs, expediting institutional review board approval of national open cooperative trials at member institutions, and facilitating enrollment of open trials through partnerships between cooperative groups and community hospitals. The guidelines on AYA oncology published by the National Comprehensive Cancer Network in 2012 emphasize all of these factors, particularly the point about clinical trial provision, access, and referral. As Albritton and Coccia stress in their article, strategies are needed to change referral patterns of adolescent patients to ensure that they are evaluated and treated at NCI-sponsored cancer centers that offer expertise in the caring for patients in their age range and with their type of cancer, regardless of whether a formal AYA program has been established.

There are newer data that collaboration between pediatric and medical oncology groups through a shared AYA oncology program within a cancer center can lead to improved trial enrollment. Between the creation of an AYA program in 2006 and the year 2010, a total of 57 patients were referred to the program at Children’s Hospital of Pittsburgh/University of Pittsburgh Cancer Institute. Patients in the age range of 19 to 22 years could choose to be treated at either the pediatric or adult facility. Nine (33%) of the 27 patients treated at the University of Pittsburgh Cancer Institute were enrolled in a trial, which was a statistically significant improvement compared with historical data from the previous 3 years. A growing number of AYA oncology programs have emerged in the United States over recent years, each with different approaches to collaboration. Some serve as a consult service available to pediatric and adult oncology teams at different centers, whereas others have their own ward and clinic space; more models will surely emerge in the future. The continued growth and expansion of such programs throughout the country should be a boon for clinical trial participation, as more and more AYA patients will have access to expertise and trials at partnering pediatric and adult medical centers. Other aspects of AYA oncology programs that have the potential to improve patient care and outcomes include shared tumor boards, shared fertility services, and psychosocial support.

Incorporating AYA oncology lectures into the education of medical students and residents, as well as continuing medical education for community oncologists, internists, pediatricians, family practitioners, and other health care providers on the topics of AYA oncology and the challenges of caring for these patients, should increase referrals and open lines of communication. This goal can be accomplished through educational symposia and Web-based modules such as ASCO University’s “Focus Under Forty: Clinical Trials for Adolescents and Young Adults” program. Another approach to increase the flow of these patients to the providers with the most expertise and clinical trial access is an aggressive local marketing campaign, directly targeting patients and families, to be undertaken by each individual program.

An obvious and essential aspect of improving clinical trial participation by AYA oncology patients is increasing the number of clinical trials available to them and increasing the number of centers where they can be enrolled in these trials. Strategies to address this issue include the evolving improved collaboration between pediatric (COG) and adult cooperative groups (SWOG, Alliance for Clinical Trials in Oncology, Eastern Cooperative Oncology Group/ American College of Radiology Imaging Network) through the newly proposed National Clinical Trials Network Guidelines; discussion of these strategies is outside the scope of the present article. Once implemented, this national plan should increase the number of AYA oncology patients aged...
To 19 years enrolled in clinical trials. This topic is also the focus of another article (by Gupta and Indelicato) being published in this Pediatrics series.

MEASURING SUCCESS

Once these strategies are employed, oncologists who care for these patients need metrics to measure their progress. Establishing shared local and national databases focusing on AYA patients should facilitate tracking of patients and monitoring their clinical trial participation. Referral to and treatment at NCI-sponsored cancer centers that have AYA expertise and clinical trial enrollment are short-term measures; disease-free and survival outcomes offer long-term data that can be measured in these patients.

CONCLUSIONS

Younger AYA oncology patients aged 15 to 19 years experience poorer cure rates overall compared with younger pediatric patients for a variety of reasons. One established factor is the paucity of adolescent patients enrolled in cooperative clinical trials, which offer cutting-edge therapy and the potential for improved cure rates. We have analyzed the available data and devised broad strategies to address the shortcomings of the current health care system. These strategies include improving the education of health care providers and patients, increasing the collaboration between pediatric and medical oncologists caring for these patients (which may include the establishment of an AYA program), and the national integration of pediatric and adult cooperative clinical trial groups. By highlighting the importance of this issue, our goal is to stimulate further action at both the local and national levels, improving clinical trial participation by adolescent patients and, by extension, older AYA patients and ultimately cure rates in this underserved population of patients with cancer.

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