

# Increasing the Number of Clinical Trials Available to Adolescents Diagnosed With Cancer

## abstract

Improving access to clinical trials for adolescents with cancer remains an important issue for pediatric health care providers. In this brief report, we highlight barriers to increasing the number of clinical trials as a mechanism for addressing this problem. The challenges discussed include: (1) engaging stakeholders to increase funding; (2) increasing cooperation between clinical trial cooperative groups; and (3) permitting delivery of novel drugs to postpubertal adolescents, in the absence of formal pediatric Phase I evaluation. *Pediatrics* 2014;133:S114–S118

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### KEY WORD

adolescent oncology

### ABBREVIATIONS

AYA—adolescent and young adult  
CIRB—Central Institutional Review Board  
COG—Children's Oncology Group  
FDA—US Food and Drug Administration  
IRB—institutional review board  
NCI—National Cancer Institute  
NCTN—National Clinical Trials Network  
NRSTS—non-rhabdomyosarcoma soft tissue sarcoma

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Adolescents with cancer have limited enrollment in National Cancer Institute (NCI)–sponsored clinical trials compared with other age groups.<sup>1,2</sup> Many factors contribute to this observation, including a relative lack of trial availability. The most common types of cancers among adolescents aged 15 to 17 years are germ cell tumors, lymphoma, sarcoma, leukemia, and brain tumors, each of which is rare among the totality of all cancers.<sup>3,4</sup> Furthermore, even if a trial is available, the delivery and toxicity of treatment protocols experienced by adolescents compared with younger children could affect outcome.<sup>5</sup> Furthermore, regardless of therapeutic appropriateness, adolescents <18 years of age are also not eligible for adult trials, thus further limiting their access. This exclusion allows adolescents to fall into the gap between therapeutic advancements in cancer treatment.

Fortunately, the median survival for many cancers of adolescents is, in fact, favorable,<sup>6</sup> necessitating adjustment of measurable outcomes from quantity of survival to quality of survival (ie, what the cost of cure has been with respect to late effects of therapy).<sup>7</sup> However, 9 of the 26 most frequent types of cancer in the adolescent age group had a 5-year survival rate of <70% (Table 1).<sup>8</sup> Cancers associated with 5-year survival rates of <50% include acute myeloid leukemia, rhabdomyosarcoma, hepatocellular carcinoma, and central nervous system tumors. Of the cancers in the 15- to 19-year-old group that are classifiable as stage IV or distant disease, 4 had 5-year survival rates of <40%: osteosarcoma, Ewing's sarcoma, rhabdomyosarcoma, and colorectal carcinoma.

In the present article, we discuss strategies to increase the number of clinical trials available to adolescents who have cancer as a way of improving their enrollment. Many aspects of this discussion are relevant to diseases other than cancer. Collectively, this issue

**TABLE 1** Five-Year Survival of 15- to 19-Year-Olds Diagnosed (2000–2004, SEER) in 18 Regions of the United States (29% of the United States) According to Cancer Type for All Stages and for Stage IV for Which There Were at Least 25 and 10 Patients, Respectively<sup>8</sup>

Rank	Cancer Type	N	Survival (%)
All stages			
1	Bladder carcinoma	23	100.0
2	Thyroid carcinoma	490	98.4
3	Fibromatous neoplasms	102	98.0
4	Melanoma	506	95.6
5	Hodgkin's lymphoma	833	94.4
6	Low-grade astrocytoma	181	92.7
7	Nasopharyngeal carcinoma	41	90.2
8	Oral cavity and pharynx carcinoma	61	90.1
9	Ependymoma	37	88.9
10	Carcinoma of the cervix and uterus	16	87.5
11	Lung carcinoma	30	86.0
12	Kidney carcinoma	30	83.3
13	Chondrosarcoma	34	82.4
14	Chronic myeloid leukemia	55	81.8
15	Intracranial germ cell tumor	146	79.3
16	Non-Hodgkin's lymphoma	522	76.5
17	Gonadal carcinoma	30	70.0
18	Osteosarcoma	249	64.1
19	Acute lymphoid leukemia	485	62.3
20	Colorectal carcinoma	69	61.5
21	Ewing's sarcoma	160	59.0
22	Medulloblastoma/PNET	93	56.7
23	Acute myeloid leukemia	248	48.4
24	Rhabdomyosarcoma	102	40.8
25	Hepatic carcinoma	29	34.1
26	Glioblastoma, anaplastic astrocytoma	78	16.4
Stage IV			
1	Hodgkin's lymphoma	140	96.41
2	Thyroid carcinoma	12	83.33
3	Chronic myeloid leukemia	38	81.58
4	Gonadal germ cell tumor	56	78.53
5	Acute lymphoid leukemia	295	63.62
6	Intracranial germ cell tumor	23	65.22
7	Non-Hodgkin's lymphoma	123	57.62
8	CNS tumor	14	50.00
9	Acute myeloid leukemia	149	47.10
10	Osteosarcoma	31	32.26
11	Ewing's sarcoma	31	32.26
12	Rhabdomyosarcoma	25	12.00
13	Colorectal carcinoma	14	7.14

CNS, central nervous system; PNET, primitive neuroectodermal tumor; SEER, Surveillance, Epidemiology, and End Results Program.

of *Pediatrics* provides a platform for pediatric and adult communities to begin to address these challenges.

## THE CHALLENGES

### Improving Funding for the Study of Rare Diseases: Engaging Funders and Stakeholders

The cost of conducting multicenter clinical trials is extraordinary and likely represents the most important barrier to the number of clinical trials available

for any age group. In the era of the “fiscal cliff,” government bodies need to be even more prudent in funding allocation. It is challenging to acquire public funding to study a rare disease in a population that has a reasonable chance of cure (eg, testicular cancer in a 16-year-old), compared with spending dollars studying hepatocellular carcinoma or lung cancer, from which thousands of adults die each year. However, others argue that the relative

number of years of life gained in studying cancers in young people far surpasses that gained in older adults with metastatic carcinomas.

The costs of running a specific trial have also substantially increased over time, in part due to the cost of novel molecularly targeted therapies and the sophisticated biological correlatives needed to measure their specific impact. With today's absence of adequate state resources, there is a need to lobby donors, philanthropy, and special interest groups to generate the infrastructure needed to develop new studies for the rarer cancers of adolescents. Funds could be channeled through specialized trial consortiums, such as the Sarcoma Alliance for Research, which offer the collective intellectual resources to refine and conduct new trials. This paradigm of specialized groups is illustrated by many new drug studies. These studies begin with basic science exploration involving the collection of rare tumor tissue samples and multifaceted efforts to discover new targets. This process is expensive and generally precedes the selection of the therapeutic agent. Selection of the agent then requires further validation of efficacy with larger and even more expensive clinical trials. To achieve accrual goals, these clinical trials must remain open for years due to the rare nature of the disease in question. In such a scenario, when return on investment is distant and improbable, commercial interest may not be reliable. Therefore, the need for state or philanthropic funding strengthens.

For all further strategies outlined in the following discussions, please assume that cost is not an issue.

### **Cooperative Groups Cooperating: Promoting Combined Studies Between Pediatric and Adult Cooperative Groups**

Cancers affecting adolescents are also prevalent in young adults who are

treated by hematologists and oncologists at adult institutions. However, there are often regulatory barriers preventing adolescents treated at adult hospitals from accessing pediatric-based therapy. Important bidirectional knowledge translation between pediatric and adult health care providers is needed to improve clinical trial design and access. For example, in acute leukemia, sequential international studies have demonstrated the value and efficacy of pediatric-based therapy for adolescent and young adult (AYA) patients with leukemia, with age-appropriate modifications to avoid undue toxicity.<sup>9,10</sup> Consequently, an adult cooperative group, Cancer and Leukemia Group B, united with the Children's Oncology Group (COG) to offer pediatric-based acute leukemia therapy to AYA patients seen by adult health care providers.<sup>11</sup> This program was a success in proving the feasibility of such an immense collaboration, offered age-appropriate therapy to AYA patients. It also offered an opportunity to examine additional age-relevant outcomes, such as adherence and toxicity, which had not previously been prospectively studied.

With rare diseases, trial availability is limited by the reality of the time required to meet accrual goals and thus trial completion. Intergroup collaboration helps to mitigate the stress of accrual by offering the same study to a larger population. For example, although non-rhabdomyosarcoma soft tissue sarcoma (NRSTS) is a common tumor among AYA patients, the relative incidence of it in the population is low. NRSTS is a cancer associated with modest survival requiring comprehensive multidisciplinary care with medical, surgical, and radiation oncologists. Currently, there is a collaborative effort between COG and the Radiation Therapy Oncology Group to design a study for patients newly diagnosed with NRSTS.<sup>12</sup>

Months of detailed discussions, dedicated physicians, time, money, partnerships, and compromise are required to embark on such projects. International collaboration represents another avenue for increasing trial opportunities for diseases of rare incidence. EURAMOS 1 (the European and American Osteosarcoma Study)<sup>13</sup> was the first attempt at a cross-Atlantic collaboration for a study in osteosarcoma, the most common bone tumor in adolescents. This partnership was an important initiative to obtain the accrual power sufficient to answer a critical treatment question in a randomized fashion that would otherwise not have been possible. More than 1800 patients aged <18 years with localized osteosarcoma were registered internationally.

Another major initiative that should improve access to and participation of adolescents with cancer in clinical trials is occurring in the United States. The NCI and the cancer community have accomplished the following: (1) consolidated the existing 10 Clinical Trials Cooperative Groups into a more streamlined NCI National Clinical Trials Network (NCTN), consisting of 4 adult and the COG, designed to meet an initial goal of speed and efficiency; (2) migrated to a common enrollment and data management system for all 3100 participating community and research institutions in the NCTN; (3) accepted an increased emphasis on clinical trial innovation, including the promotion of biologically focused Phase II clinical trials and the incorporation of companion diagnostics and translational science, predicated on the collection of clinically annotated biospecimens; (4) revamped the clinical trials prioritization process; and (5) initiated a concerted promotion of increased participation in cancer clinical trials.<sup>14</sup>

Another initiative in the United States that should be helpful is the requirement that all sites in the NCTN use

the centralized NCI Central Institutional Review Board (CIRB)<sup>15</sup> and the development of a separate NCI CIRB for early-phase studies in adult patients.<sup>16</sup> The NCI CIRB is assuming more functions and responsibilities of local institutional review boards (IRBs) in the development of the independent CIRB model; this action should also facilitate clinical trial development, access, and participation by potential participating patients of all ages.<sup>15,17</sup>

In Europe, there is no equivalent to the NCI, and the European Organisation for Research and Treatment of Cancer serves in part as one of the very few pan-European research groups.<sup>12</sup> The current European Clinical Trials Directive is attempting to harmonize and standardize the procedures for clinical trial approval and conduct but has encountered major obstacles; in addition, central infrastructural funding is lacking.<sup>14</sup>

### Phase I Testing of Select Drugs Should Be Offered to Adolescents Without the Need of a Formal Pediatric Evaluation

Phase I studies examine toxicity and tolerability of novel anticancer drugs and are available to those  $\geq 18$  years of age. Adolescents  $< 18$  years of age are not permitted enrollment into adult Phase I studies, and they therefore do not have access to these drugs until a formal Phase I evaluation is complete in children. Barriers to new drug evaluation in pediatrics are numerous and include predicted longevity of the agent, approved indication in adult cancer, industrial assurance of ongo-

ing drug development, conduction of pediatric Phase I studies, and funding. Permitting access to adult Phase I evaluation of novel drugs to postpubertal adolescents (eg, age  $\geq 15$  years) would then permit accrual to subsequent Phase II studies involving the respective new drug. Access to Phase II and II studies would substantially increase trial availability to adolescents with advanced cancers. There are many legal and ethical issues surrounding the expansion of novel drugs to adolescents which may not end up acquiring market longevity; these are topics beyond the scope of the present article.

The US Food and Drug Administration (FDA) is investigating whether drug handling among adolescents is different from adults.<sup>18</sup> At the time of submission of the present article, the FDA had not accepted the recommendation of its Pharmaceutical Science and Clinical Pharmacology Advisory Committee to lower the age of Phase I and II trials to  $< 18$  years (given that the drug clearance in adolescents is the same as in healthy adults). The FDA is currently evaluating recommendations regarding the Guidance for Industry for Pediatric Clinical Pharmacology (Y. Waples PharmD, personal communication, 2012). It is possible that because the age of consent is 18 years in the United States, enrollment into “experimental” drug studies, such as Phase I trials, cannot occur with surrogate consent (ie, from parents). Interestingly, in Canada, there is no defined age of consent. If the FDA accepts the advisory committee’s recommendation, the new NCI Adult

CIRB that will manage Phase I and II clinical trials, and that every NCTN site will have to use, should have synergistic beneficial effects for clinical trial participation of future adolescents with cancer.

### CONCLUSIONS AND RECOMMENDATIONS

Increasing the number of clinical trials for older adolescents with cancer is a complex initiative that will involve important cultural shifts among stakeholders, government, and industry. However, recent initiatives in the United States and Europe should set the stage for precedents in this regard, and we look forward to the next 5 years of ongoing change. The earliest impact should be centralization in the United States of all national cancer clinical trial accruals and data management. The next most likely benefit will be the centralization of IRB processes of all national cancer clinical trials instead of the current local IRB management at 3100 participating community and research institutions in the NCTN. In Europe, it is critical that the ongoing revision of this European Clinical Trials Directive ensures more effective clinical trial activity, with the goal of enabling cancer clinical trials and translational research activity in Europe from being compromised.<sup>14</sup> Finally, as our knowledge of drug handling improves, translating newly acquired information into changes in policy, such as lowering the age limit to  $< 18$  years for novel therapeutic agents, will be instrumental.

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