Older Adolescents and Young Adults with Cancer, and Clinical Trials: Lack of Participation and Progress in North America

Archie Bleyer • Troy Budd • Michael Montello

Contents

5.1 Introduction

Whereas the survival longevity benefits of a clinical trial to an individual may be debated [1], there is no question about the value of clinical trials to subsequent generations and to society in general. There is no benefit from the knowledge and experience gained from clinical trials if they are not conducted. In addition, clinical trials are required for new agents to receive federal approval, and for practices to become accepted as standards of care and, after publication, to be disseminated to community practices.

On the side of the personal benefit derived from participation in clinical trials, studies in children have indicated a survival advantage to children enrolled on clinical trials for acute lymphoblastic leukemia (ALL) [2], non-Hodgkin lymphoma [3], Wilms tumor [4], and medulloblastoma [5]. In the United States and Canada, a comparison of 16- to 21-year-olds with ALL or acute myeloblastic leukemia (AML) showed that the outcome was superior in patients treated on CCG trials than in those not entered [6]. Moreover, personal benefit from clinical trial participation may well accrue, especially with regard to quality of life during and after clinical trials.

One example of the benefit of adolescent and young adult participation in clinical trials comes from the recent retrospective comparisons of clinical trials in adolescent and young adult ALL patients. Prior population-based analyses suggest that increasing age was a poor prognostic factor in patients with ALL, but the reason for this correlation is unclear. Three indepen-

dent groups – in France, the United States and The Netherlands – have extracted retrospectively the data on adolescent and young adult patients who enrolled on either a pediatric or adult clinical trial for ALL. Strikingly similar results were found in all cases: the pediatric regimen resulted in superior outcomes – nearly twice the event-free and overall survival rates – to the adult leukemia trials extant at the time [7–9]. Factors that might contribute to outcome (French-American-British, FAB, classification, presenting white count, cytogenetics) were collected prospectively on the clinical trials and essentially excluded as confounding reasons for decreased survival. Thus, treatment effect has been the favored explanation for the observed differences. In addition, the older adolescents and young adults who participated in the trials were given an opportunity for substantial personal benefit and not just altruism to help succeeding patients of similar age.

This chapter summarizes the evidence for low participation rates of older adolescents and young adults with cancer on clinical trials in the United States. Possible reasons for this are reviewed, and a correlation is described between the lack of clinical trial participation and the relatively worse improvement in survival in adolescent and young adult patients compared with younger and older persons. The overriding premise is that to increase our understanding of cancer in this population and improve outcomes, the rate of clinical trial enrollment of adolescent and young adult cancer patients must be enhanced.

5.2 Deficit in Adolescent and Young Adult Participation in Clinical Trials

As Fig. 5.1 implies, the participation rate of 15- to 19-year-olds in the United States on national cancer treatment trials sponsored by the National Cancer Institute (NCI) during the period 1997–2003 was approximately half that of the corresponding rate in those under 15 years old [10–14]. In 20- to 29-year-olds, it was approximately 15% of the rate in children under 15 years old. With the exception of the most elderly (over 85 years of age), 20- to 29-year-olds are the age group with the lowest clinical trial participation.

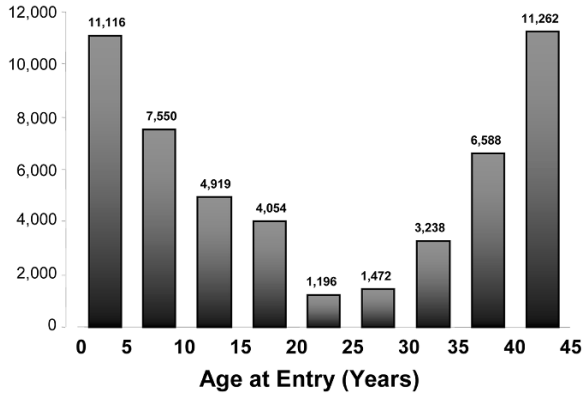

Figure 5.1

Entries of 51,395 patients <45 years of age onto United States National Cooperative Group treatment trials (sponsored by the Cancer Therapy Evaluation Program of the National Cancer Institute Division of Cancer Treatment and Diagnosis) during the period 1997–2003, inclusive. Modified from Bleyer [26]

5.2.1 Race/Ethnicity

A decrease in the participation of minority adolescent patients in clinical trials is not a reason for this deficit in participation, however. In fact, in the United States, minority children and adolescents with cancer show equal or higher rates of entry onto national clinical trials [14]. Figure 5.2 shows the race- and ethnicity-specific accrual for each 5-year age interval from 0 to 40 years of age [12]. The accrual pattern relative to age is similar among all racial and ethnic groups. Specifically, the rate of inclusion of older adolescent patients is lower for non-Hispanic whites, Hispanics, African Americans, Asians, native Indians, Alaskan natives, and Hawaiian and other Pacific Islanders than in the other age groups within their racial or ethnic group. In terms of absolute participation rates as a function of ethnic or racial group, the rate in Hispanic patients is less than one-fifth the rate in white patients, the rate in African-Americans is one-tenth the rate in white patients, and the rate in Asians, native Indians, and Alaskan natives is each about 1% of the rate in white patients (Fig. 5.2) [12]. This suggests that even though the overall nadir pattern is similar across the races and ethnicities evaluated, the relative knowledge gained may well be less in

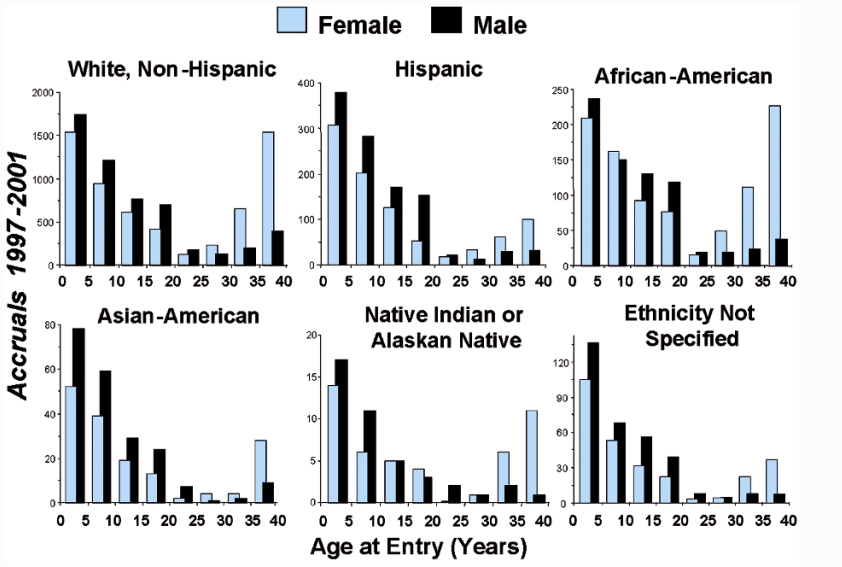

Figure 5.2
Accrual of patients <45 years of age to cooperative group treatment trials by race/ethnicity as a function of age at entry, during the period 1997–2001, inclusive. Modified from Bleyer [26]

the minority populations since there are fewer opportunities to learn about the racial and ethnic differences in the disease and its management.

5.2.2 Gender

The nadir in the clinical trial participation rate at 20–29 years of age is apparent in both females and males, but it is considerably more striking in males (Fig. 5.2). This is the case for all ethnic and racial groups specified above (data not shown).

5.2.3 Residence

Geographically, this gap has been observed throughout the United States and is in striking contrast to the accrual of a majority of patients under 15 years of age to clinical trials in virtually all metropolitan and rural areas across the country [14].

5.2.4 Individual Types of Cancer

Analysis of clinical trial participation broken down by individual types of cancer (i.e., sarcomas [15], leukemia [16], lymphoma [17], brain tumors [18, 19], and breast cancer) showed that participation was once again less in those aged 15 to 29 years than in those in younger or older age groups (Fig. 5.3).

5.3 Current Trends in Clinical Trial Participation by Older Adolescents and Young Adults with Cancer

Unfortunately, a downward trend in the accrual of patients 15–29 years of age onto United States National Cooperative Group treatment trials sponsored by the United States NCI was apparent from 1997 to 2003. The proportion of all patients entered onto the national phase I, II, and III treatment trials declined from 5.5 to 2.5% over this interval. This ominous trend may have been reversed in 2003 as a result, at least in part, of the Children's Oncology Group Initiative described below.

5.4 Reasons for the Lack of Clinical Trial Participation by Older Adolescents and Young Adults with Cancer

The reasons for the gap in the participation of older adolescents and young adults in clinical trials are to a large extent unknown and are undoubtedly multifactorial. The reasons that were identified at an NCI-sponsored workshop on the topic and further developed in subsequent evaluations [20, 21] are summarized in Table 5.1.

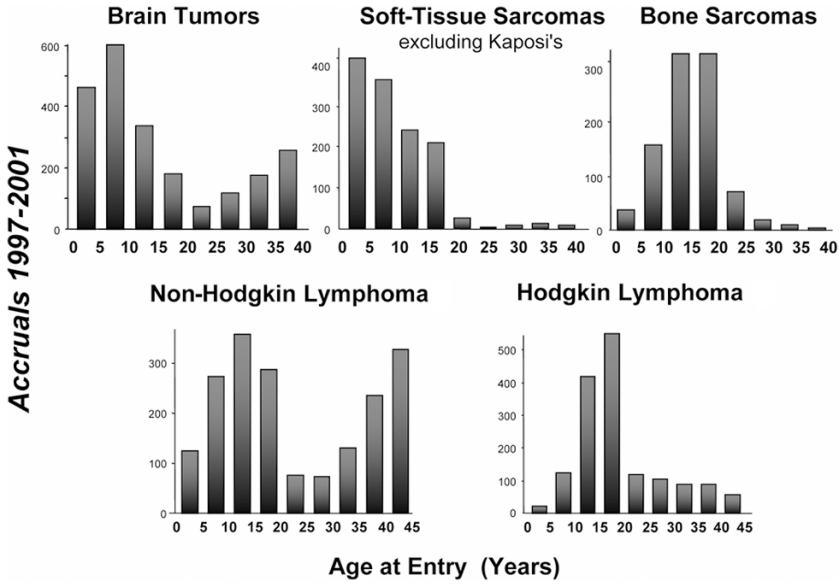

Figure 5.3

Accrual of patients <45 years of age to cooperative group treatment trials by cancer type as a function of age at entry, during the period 1997–2001, inclusive. Modified from Bleyer [26]

A patient between 15 and 29 years of age with newly diagnosed cancer is more likely to be thrust into a state of limbo – both medically and socially – than either a child or an older adult with cancer. Thus, it is no surprise that patients with cancer in this age group are less likely than either younger or older patients to find their way to a clinical trial that could improve their chances of a better outcome. They are less likely than younger patients to find their way to centers that offer clinical trials. Fewer patients in the 15- to 29-year age group are referred to dedicated, comprehensive cancer centers than patients in any other age group, with the possible exception of patients in the most elderly age group (>85 years) [12]. In particular, in the United States, more than 90% of children with cancer who are under 15 years of age are managed at institutions that participate in NCI-sponsored clinical trials. In contrast, only 20–35% of 15- to 19-year-olds with cancer are managed at such institutions [13, 14]. Among 20- to 29-year-olds, the inclusion rate is even lower, with fewer than 10% being treated at institutions that are members of cooperative groups, either pediatric or adult. In adult cancer patients over 40 years of age, the corresponding rate is approximately 20%, including community cancer centers that participate in NCI-sponsored clinical trials (community clinical oncology programs).

The American College of Surgeons (ACoS) has tracked 15- to 19-year-old patients in the ACoS Tumor Registries who were referred to centers that participated in Children's Cancer Group (CCG) or Pediatric Oncology Group (POG) trials. In their National Cancer Database report, those patients 15–19 years of age who were treated at CCG and POG sites with non-Hodgkin lymphoma, liver cancer, ALL, AML, osteosarcoma, or Ewing sarcoma had better 5-year survival rates than those treated elsewhere [22]. However, there were no differences in the 5-year rates for patients with two cancers associated with an excellent outcome, Hodgkin lymphoma and testicular carcinoma, or with brain tumors, one of the cancers associated with the worst prognosis.

Another reason for this deficit is a lack of treatment regimens and clinical trials for young patients. Between 1 and 70 years of age, the age group with the fewest therapeutic cancer trials available to it has been the 15- to 40-year age group (NCI Clinical Therapy Evaluation Program data).

Yet another reason for the deficit in the enrollment of adolescents and young adults with cancer onto clinical trials is that the spectrum of cancers in them differs from that of any other age group. Hence, there is no organized body of research that is dedicated to the spectrum of cancers that affect this age group.

Table 5.1 Potential barriers to participation of older adolescents and young adults in clinical trials

Potential barriers to participation of older adolescents and young adults in clinical trials

Continuity of Care and Philosophy

- Older adolescents and young adults have the lowest rate of primary care use of any age group.
- Adolescents and young adults are more likely than younger children to lack a usual source of care. Without a primary physician whom the patient knows, the patient may be reluctant to trust the medical establishment and the clinical trial enterprise.
- Physicians and other healthcare professionals are either poorly trained or unwilling to care for adolescents.
- Adolescents and young adults aren't "supposed to" have cancer. As a result, clinical suspicion is low, and symptoms are often attributed to physical exertion, fatigue, trauma, and stress.
- Adolescents and young adults have a strong sense of invincibility. Out of denial, they may delay seeing a physician about symptoms. Even when seen, they may give poor historical information, especially to a physician untrained to "read between the lines" of a young person's history.

Economic and Insurance-Based Factors

- In the United States, young adults are the most uninsured and most underinsured age group. Nearly half of all 15- to 19-year-olds lose the healthcare insurance provided by their parents and do not acquire adequate coverage at their next destination in life, whether at an institution of higher learning, through an employer, or by independent means.
- Treating physicians may be reluctant to promote the enrollment of adolescents or young adults onto clinical trials because of the time, cost, and effort involved, not only on their part (and that of their team), but also on the part of the patient and family.
- Health insurance organizations may deter the referral of adolescents and young adults to a cancer center or cooperative group or entry onto clinical trials. Attendees had little direct evidence of this factor, however.

Provider Bias

- Coping with older adolescents and young adults with cancer is difficult in general. The additional burden of clinical trial participation is therefore heavier for adolescents than for younger or older patients.
- Treating physicians may be reluctant to refer adolescent and young adult patients to clinical trials because they perceive these patients as likely to be noncompliant (or nonadherent) with the protocol requirements. These patients are perceived to have enough difficulty complying with the treatment plan and keeping up their lives, without the additional burden of protocol obligations.
- Oncologists (surgeons, radiotherapists, medical oncologists, gynecologists) in private practice may retain these patients rather than refer them to a tertiary-care facility or cooperative group member institution.
- Providers may be biased against clinical trials in adolescents and young adults. Reasons may include the historically better results of standard treatments in adolescents and young adults than in older and younger patients, and the additional effort of entering someone in the age group onto a clinical trial, including having to explain and obtain consent to study entry from both the patient and family.
- Family practitioners, gynecologists, and internists may not regard multimodality therapy as important in older adolescents and young adults as in younger and older patients. Reasons may include the greater use of single-modality therapy in patients in this age range, the additional burden of coordinating multidisciplinary care in the age group, and the historically better results obtained in this age group than in older patients.
- Providers may be unaware of opportunities for clinical trial participation for adolescents and young adults with cancer.

Table 5.1 *(continued)*

Potential barriers to participation of older adolescents and young adults in clinical trials

Patient/Family Preferences

- Adolescent and young adult patients and/or their parents are more inclined to refuse referral to a cooperative group member institution or to be entered onto a clinical trial.

Provider Age Policies

- The age policies of hospitals may prevent patient access to clinical trials that are under way at the institution. Children's hospitals may have upper age limits that deny the admission of older patients or deny clinical privileges to the treating physician. The reverse may be true for younger patients accessing clinical trials primarily intended for adult patients.
- The clinical trial itself may have age limits that prohibit the entry of an otherwise eligible patient.

Cooperative Group and Cancer Center Limitations

- Pediatric and adult cooperative groups and cancer centers may not allow the enrollment of adolescent and young adults onto clinical trials because of restrictive eligibility criteria.
- A clinical trial may not be available.
- Adult cooperative groups and cancer centers may lack treatment protocols for younger patients.
- Pediatric cooperative groups and hospitals may lack treatment protocols for older patients.
- Clinical trials for the types of cancer that predominate among adolescents and young adults may not be a priority of the cooperative group enterprise.

Adding to this problem is the fact that there is no discipline in medicine devoted to this group. Neither pediatric oncologists nor oncologists who care for adult patients are trained – certainly not optimally – for this set of diseases. Moreover, even those diseases that appear to be the same often have biologic differences. For example, adolescents have different forms of leukemia than either younger or older persons. In particular, the biologic characteristics (and prognosis) of ALL change dramatically in postpubertal patients. Different biologies, likely to respond differently to therapeutics, might best be studied in dedicated and separate clinical trials.

5.5 Survival and Mortality Rates in Adolescents and Young Adults with Cancer

Cancer mortality and survival trends in the United States in 15- to 29-year-olds are behind the gains made in younger and older persons [10–12]. This is particularly true for 20- to 29-year-olds, but it is also apparent for 15- to 19-year-olds [13].

5.5.1 Survival Improvement: From Peak to Nadir

The annual improvement in the 5-year survival rate from 1975 to 1997 averaged 1.5% per year in children under 15 years of age and 1.7% per year in adults 50–85 years of age (Fig. 5.4) [23]. In 15- to 24-year-olds, however, the improvement averaged 0.75% per year, and in 25- to 34-year-olds, there was no perceptible improvement (Fig. 5.4). In the mid 1970s, when national cancer survival rates became available, the 5-year cancer survival rate for Americans was higher in the 15- to 29-year age group than it was in younger or older persons. If the trend of 1975–1997 is projected to 2005, the 5-year survival rate is now lower in the young adult age group than it is in younger and older persons. In a quarter of a century, what was an advantage to be diagnosed with cancer during early adulthood has become a relative disadvantage. To compound matters, the affected population has steadily increased as the "baby boomers" traverse this age range.

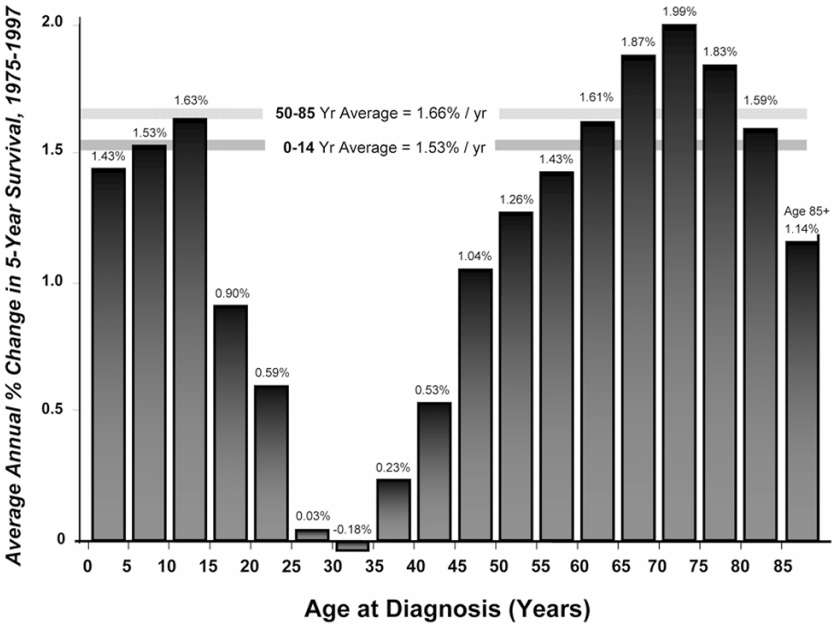

Figure 5.4

Average annual percent change in the 5-year survival rate of patients with invasive cancer who were in the United States Surveillance, Epidemiology and End Results (SEER) registry from 1997 to 2001. Data from the National Cancer Institute SEER program, courtesy of Lynn Ries [26]

5.5.2 Survival by Gender and Ethnicity/Race

These ominous trends in survival prolongation among 15- to 29-year-olds are apparent in both males and females, with males showing a greater deficit than females (Fig. 5.5).

5.5.3 Survival by Individual Types of Cancer

These trends have also held true for individual types of cancer, including sarcomas [8], brain tumors (astrocytomas, ependymomas, and other gliomas) [11], leukemia [9], lymphomas [10], and breast cancer. Although 15- to 29- year-olds with leukemia did not have a nadir in outcome improvement, they did have a worse mortality rate relative to their incidence than that of any other age group [9].

5.5.4 Correlation of Survival Improvement and Mortality Reduction

The age-dependent trends in survival improvement are reflected in the age-related trend of reduction in the national cancer mortality rates (Fig. 5.6). For cancer patients younger than age 40 years, the nadirs are 25–29 years and 30–34 years, respectively, with the nadir for mortality reduction expected to be at an older age than that for incidence, since the effect on death would occur later than the effect on survival before death. This correlation also validates the SEER measurements based on a sample of approximately 13% of the United States, whereas the mortality data are for all deaths in the country.

5.6 Why the Lack of Progress in Older Adolescents and Young Adults with Cancer?

Absolute differences in survival between younger patients and adolescent and young adult patients are probably due to a combination of biologic and therapeutic differences, some immutable. However, the marked disparity in survival improvement over time suggests mutable changes disproportionably rendered.

Proposed explanations apply to the patient, healthcare profession, family/community, and society/culture in general [24]. The patient category can be subdivided further into biologic/physical, psychologic/emotional

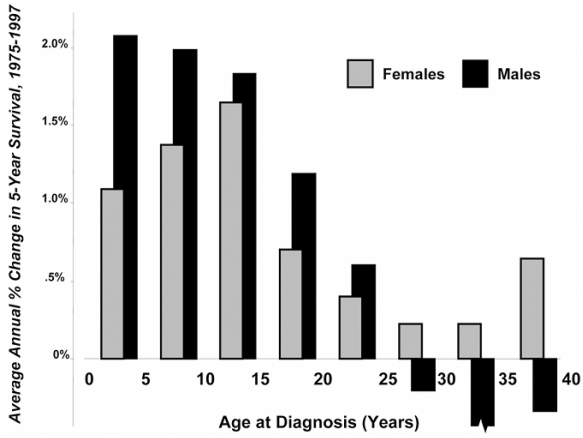

Figure 5.5

Comparison in males and females with invasive cancer of average annual percent change from 1975 to 1997 in the 5-year survival rate (United States SEER program). Modified from Bleyer [26]

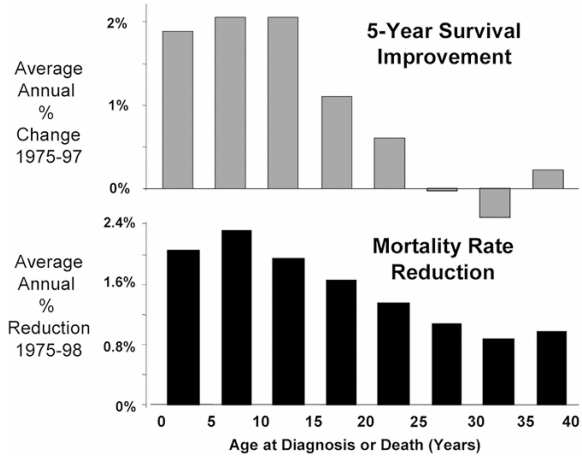

Figure 5.6

Correlation of national cancer mortality rate reduction in the United States as a function of age at death, with the rate of improvement in survival duration as a function of age at diagnosis (data from the United States Census Bureau and United States SEER program)

spiritual, economic/financial, and social factors. Biologic factors include the unique physiologic and pharmacologic characteristics of adolescent and young adult patients and their cancers. The health-care profession explanation includes a lack of awareness by general healthcare providers and of training, knowledge, and experience by oncology specialists. There is no other age during which the time to diagnosis is longer, fewer tumor specimens are available for translational research, or clinical trial participation is lower [11]. The family/community category involves family members and knowledge workers who lack awareness of the problem. Societal issues consist of the challenges societies face in providing for adolescent and young adult healthcare needs. Institutions of higher learning do not have cancer awareness as an essential educational or health evaluation component.

The issue of clinical trial participation seems paramount, since failure to investigate a disease in an age group in which it is prevalent or different is likely to limit the progress that can be made in that group. "No research, no gain" is the explanation. In the United States, the pace of improvement in the 5-year survival rates from sarcoma over the past quarter century has been far less above age 15 years than in younger patients, and this age-dependent pattern is statistically correlated with the rate of clinical trial activity [8]. A report from Australia documented a sharp falloff in bone sarcoma patients entered onto clinical trials above age 15 years, in association with a drop in survival rate [25].

Although the correlation of outcome improvement with clinical trial participation is not proof of a cause-and-effect relationship, there are reasons to believe that failure to study cancer therapies in specific age subgroups does explain, at least in part, why progress in the age group has fallen behind that achieved in other age groups that have had higher rates of clinical trial participation. The correlation of outcome improvement with clinical trial participation underscores the value of clinical trials in cancer research.

The above considerations suggest several solutions:

1. Societal/cultural: improve awareness of the adolescent and young adult cancer problem.

2. Family/community: improve awareness and health-care insurance to reduce delays in diagnosis and permit participation in clinical trials.
3. Professional: increase awareness and training, and the availability, importance and utilization of clinical trials [15].
4. Personal/patient: overcome invincibility ideation and emphasize importance of health-care and health-care insurance. Another conceptual approach to overcoming the barriers to clinical trial participation faced by adolescent and young adult patients is provided in Table 5.1.

Reversing the trend and allowing older adolescents and young adults to catch up with the progress made in younger and older patients will require a comprehensive effort by multiple organizations, including the federal government, the insurance industry, service groups, the clinical trials cooperative groups, the pediatric academic societies, community agencies, and health-care providers. A multipronged approach to problem solving will be required, beginning with public and professional awareness initiatives such as this report.

In 2000, the Adolescent and Young Adult Initiative of the Children's Oncology Group and the NCI was established as a means to increase the enrollment of adolescents and young adults in cancer clinical trials. This initiative aims to bring advances in cancer education, prevention, and treatment – including educational, social, and emotional development – to this segment of the North American population, and to member sites in Australia, New Zealand, and Europe, whose progress in cancer outcome has fallen behind that achieved in younger and older patients.

The initiative includes several strategies. In all of the pediatric group protocols for malignancies that substantively overlap young adult patients, such as leukemia, Hodgkin lymphoma and the sarcomas, the upper age limit has been raised to 30, 40, or 50 years, depending on the disease. The pediatric group has also opened adult cooperative group trials in melanoma. Reciprocally, an adult cooperative group has opened the pediatric cooperative group trial in Ewing sarcoma. Plans are underway for the pediatric and adult groups to develop and open trials together in other sarcomas. Other targets for mutual development include ALL, Hodgkin lymphoma, non-Hodgkin lymphoma, and hepatic cancer.

5.7 Summary

Cancer in adolescents and young adults has unique features; this is in addition to the special medical, physical, psychological, and social needs of patients in this age group. The spectrum of malignant diseases in this age group is also different from that in other age groups, and it is strikingly different from that in older persons. At the same time, more young people between 15 and 25 years of age have been diagnosed with cancer than children under 15 years of age, and during the past 25 years, the incidence of cancer in 15- to 29-year-olds has increased faster, and the reduction in cancer mortality has been lower than that in younger or older patients. Whereas it was once a relative advantage to have cancer during the adolescent and young adult years, patients in this age group are now behind patients in other age groups – orphaned in the world of cancer care delivery.

In the United States, older adolescents and young adults with cancer are underrepresented on clinical trials of therapies that could improve their outcome. This pattern is true for both males and females of all ethnic and racial groups. Simultaneously, the survival and mortality rates in these patients have mirrored the clinical trial accrual pattern, with little improvement compared with younger and older patients. This suggests that the relative lack of participation of adolescent and young adult patients in clinical trials has lessened their chances for as good an outcome as those enjoyed by patients in other age groups. The implication is that future progress in the treatment of the cancers among 15- to 29-year-olds will depend largely on increasing their participation in clinical trials. Regardless of whether there is a causal relationship, the impact of low clinical trial activity on furthering our scientific knowledge and management of cancer during adolescence and early adulthood is detrimental.

Thus, the increased availability of and participation in clinical trials is of paramount importance if the current deficits in outcome in young adults and older ado-

lescents are to be eliminated. Eliminating the survival deficit will require a broad initiative to increase clinical trial participation. Ultimately, a new discipline is probably in order to meet the needs of these young patients: adolescent and young adult oncology. These patients deserve trained care providers, specialized clinics and inpatient units, and probably most importantly, dedicated research strategies that are not available through either pediatric or adult care programs.

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