How NCCN Guidelines Can Help Young Adults and Older Adolescents With Cancer and the Professionals Who Care for Them

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Abstract

From 1975 to 2009, adolescents and young adults with cancer in the United States had less mortality reduction and survival improvement than either children or older adults with cancer. An NCI Progress Review Group (PRG) convened in 2005 issued a variety of recommendations to overcome the lack of progress, including the establishment of care guidelines. The outcome of 15- to 39-year-olds with cancer in the United States in 2009 was ascertained from the SEER registry, and the first guidelines for this age group, presented by NCCN, were reviewed. For the first time, the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Adolescent and Young Adult Oncology provide specific algorithm-based care recommendations for 15- to 39-year-olds with cancer, who as an age group have the greatest potential patient-years of life to be saved. A special emphasis on psychosocial evaluation and care is included, commensurate with the unique needs of persons in this age group. Although how widely the NCCN Guidelines will be used remains to be seen, they are timely, comprehensive, responsive to the NCI PRG recommendations, and a valuable resource for medical oncologists, hematologists, gynecologic oncologists, oncologic surgeons, and pediatric oncologists who care for patients between 15 and 40 years of age. A patient version will have mutually beneficial effects for families and professionals. (JNCCN 2012;10:1065–1171)

Background

In this past spring of 2012, 2 new sets of NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) were published directed at the adolescent and young adult (AYA) population with cancer: those for Adolescent and Young Adult Oncology (AYAO; available in this issue and at NCCN.org) and Acute Lymphoblastic Leukemia (ALL; to view the most recent version of these guidelines, visit NCCN.org). This overview attempts to answer 4 basic questions about the AYAO guidelines: why are they necessary, why now, how can they help, and will they matter? Because the NCCN Guidelines for ALL were released at the same time and focus specifically on AYA patients, ALL is the disease site used to illustrate the answers.

Methods

Incidence, death rates, and average annual percent change data as of 2009 were obtained from the SEER registry via SEER*Stat version 7.0.4. For patient-years of life affected, data were also applied from the US population census via DataFerritt and the SEER registry. Specific recommendations for addressing the AYAO challenges were obtained from the Progress Review Group (PRG) report on AYA Oncology (AYAO PRG), co-sponsored by the NCI and the Lance Armstrong Foundation. The AYA age range was defined as 15 to 39 years of age inclusive, per the AYAO PRG.

Results and Discussion

Why Are the Guidelines Necessary?

Table 1 shows that for the most recent year of SEER data (2009), the incidence, survival, and mortality rates of AYAs with cancer continue to represent a critical national issue. Nearly 70,000 15- to 39-year-old Americans were diagnosed during this year and nearly 10,000 died of cancer. The ratio of the cancer death rate to cancer incidence was 0.14, implying that at steady state, approximately 1 in every 7 cases in the age group...
was fatal. Of all newly diagnosed cases of cancer, 5% occurred in AYAs. Cancer was the cause of death in 10% of all deaths (all causes) and 18% of all deaths from disease (accidents and homicides excluded) in AYAs. AYA females were 1.6 times more likely than males to be diagnosed with cancer, but males and females were equally as likely to die of cancer. Among females in the age group, 24% of all deaths from disease (1 in every 4 deaths) and nearly 16% of all deaths were from cancer. Among males in the AYA age group, the ratio of the cancer death rate to cancer incidence was 0.18, indicating that at steady state approximately 1 in every 6 cases of cancer in males was fatal.

Figure 1 shows the increase in the 5-year relative survival rate in the United States during the 3 decades since 1975. Compared with the first half of the 3 decades (1975–1988), the average annual percent improvement in the survival rate declined during the second half (1989–2003). The lack of recent progress is particularly evident in 15- to 25-year-olds, whose survival prolongation has slowed such that currently this is the only age group younger than 75 years lacking a statistically significant increase. The 5% proportion of all cancer that occurs in 15- to 39-year-olds mentioned earlier is compared in Figure 1, with fewer than 1% among children younger than 15 years of age, and 78% in 40- to 79-year-olds and 46% in 50- to 69-year-olds, all of whom have had greater progress in survival prolongation since 1989 than AYAs.

Figure 2 depicts the patient-years of life affected in the United States according to specific types of cancer and age groups over the entire human age span, as estimated from the incidence of cancer as a function of year of age at diagnosis versus the remaining expected lifespan in the general population. More than 3 million patient-years-of-life were affected by the diagnosis of cancer among 15- to 39-year-olds in the United States during 2008. Cancer in AYAs ranks fourth when compared with all individual cancers and affects more than 4 times the patient-years of life of children and young adolescents, despite only 5% of all cancer being diagnosed (Figure 2 inset; yellow highlight) in AYAs.

Another factor is that the AYA age group has the highest proportion, estimated at 90%, of patients remaining in their community of residence for treatment rather than being referred to a secondary or ter-
However, their types of cancers are distinctly different from those in older persons and sufficiently less common compared with cancers that most medical oncologists are experienced in treating. Surveys at the last 3 NCCN Annual Meetings (2010–2012) reveal that most oncologists queried did not realize that AYAs with cancer have not shown the dramatic improvement seen in younger and older patients (personal communication, Peter Coccia, MD). If any particular age group should be targeted for guideline development, AYAs seem to be the most likely candidates.

Finally, the psychosocial needs of AYA patients are among the most difficult to meet of all age groups. The extraordinary array of emotional, physical, educational, financial, and spiritual challenges experienced by AYAs are arduous enough, without having to deal with a potentially fatal disease. Many oncologists are challenged by the additional complexities of psychosocial issues in AYAs. Fortunately, and as demanded by the age group, the NCCN Guidelines for AYAO specifically and more comprehensively address psychosocial needs than any other NCCN Guideline published to date.

**Why Now?**

Treatment guidelines for AYA cancer patients were recommended 7 years ago by the AYAO PRG in Executive Recommendation 4: “ensure excellence in service delivery across the cancer control continuum”:

The AYAO PRG urges the implementation of 2 principal strategies to improve service delivery to AYAs with or at risk for cancer and ensure excellence in care across the cancer control continuum. First, standards of care for AYA cancer patients must be developed, evaluated, and disseminated. This enormous task must be undertaken with the understanding that standards are dynamic and must be updated as advances in care are achieved. Excellence in care may vary not only by cancer diagnosis but by multiple other variables (eg, age and gender, race/ethnicity/culture, socioeconomic status, access to/source of care, insurance status)
that must be addressed to meet the complete spectrum of patient needs.

Second, establishing, disseminating, and reinforcing standards of cancer care for AYAs will require the ongoing and concerted collaboration of a diverse array of stakeholders. Health care providers, research sponsors, investigators, regulators, insurers, and patient advocates should expand existing collaborations and establish a national network of a coalition committed to improving the quality of life and outcomes for AYAs with cancer.

The AYAO PRG reported that referral patterns for AYAs with suspected or diagnosed cancers vary widely into a “no man’s land” between pediatric and adult oncology comprising pediatric, adult medical, radiation, surgical, or gynecologic oncologists. Most AYAs are treated in the community rather than in cancer centers, but a

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**Figure 2** Patient years of life affected by the diagnosis of cancer by type of cancer and within age groups in the United States in 2004. Data from the US population census via DataFerritt and the SEER 17 registry via SEER*Stat version 6.6.2.
robust community oncology and primary care infrastructure currently does not exist to enable patient data collection and aggregation that would support research efforts.

Another reason is the confluence of the guidelines with the publication in November 2010 of position statements from the LIVESTRONG Young Adult Alliance. These position statements discuss the need for education regarding standards of care and processes to deliver that care. They emphasize the need to promote quality care for AYAs through encouraging cognizance of the unique psychosocial context for AYA growth and development, and assessment of and attention to cognitive, psychiatric, and psychosocial issues. Other AYA-specific needs that are addressed include facilitation of the transition to treatment and suggestion of age-appropriate information and support services. In each case, the NCCN Guidelines for AYAO provide specific recommendations.

Why has it taken so long to establish the guidelines that NCCN now has provided? The PRG noted that inconsistency in treatment and follow-up care, coupled with insufficient research data, has prevented the development of guidelines for treating and monitoring AYAs with cancer, and few tools exist to measure the efficacy of treatment and psychosocial interventions delivered in diverse settings.

How Can the NCCN Guidelines Help?
First, when implemented, the NCCN Guidelines can help accomplish the AYAO PRG recommendations. They have the potential to address the challenges described earlier and overcome the deficits in survival prolongation and mortality reduction. Second, as shown in Figure 3, they emphasize more explicitly than previously published guidelines the importance of clinical trials in the age group with the lowest clinical trial activity. One of the first steps in the NCCN Guidelines for both AYAO and ALL is to consider clinical trials (Figure 3A, B), with referral to a cancer center with expertise in treating AYAs with cancer that has access to available clinical trials. For cancer in general, this action seems to be recommended for consideration even before emergency therapy (Figure 3A). Third, the biologic specimens for translational research may be increased as cancer center referral and increased clinical trial activity occurs. Finally, consistency of treatment and follow-up care may be achieved at a national level in an age group that is more heterogeneously treated than any other.

The NCCN Guidelines for AYAO also address 3 of the 4 critical elements on which quality care of AYAs with cancer depend.

First, the guidelines provide algorithms for initiation of treatment, promotion of adherence, and follow-up. Second, they specifically recommend access
to health care professionals who possess knowledge specific to the medical and psychosocial needs of this population. Third, they promote research that will ultimately provide objective evidence for improved AYA oncology care.

Finally, the guidelines for AYAO can be cited within NCCN’s cancer-specific guidelines for those cancers that occur in AYAs. The existing guidelines most affected by this potential are those with the worst the survival rates and/or the least progress: cervical cancer, non-Hodgkin’s lymphoma, bone cancer, soft tissue sarcoma, testicular cancer, ovarian cancer, thyroid carcinoma, brain cancer, acute myeloid leukemia, and ALL.11 As is now possible with the new NCCN Guidelines for ALL, this cross-guidelines capability should enable future editions of existing and new cancer-specific guidelines to be more expeditious and AYA-applicable.

**Will the Guidelines Be Used?**

After 40 years of academic medicine, I moved in 2005 from 1 of the 3 founding institutions of NCCN (The University of Texas MD Anderson Cancer Center) to a community-hospital, private-practice environment. The past 7 years have taught me that the NCCN Guidelines are extensively used by community oncologists, including reference to them at most weekly Tumor Boards, and that we should therefore be optimistic about the AYAO guidelines. However, I sense that my colleagues will not consider them important enough to follow with the same avidity that they do for the cancers of their middle- and older-aged patients. Why the pessimism? In part, they prefer to focus more on guidelines for specific cancer treatment than on those supportive care. Rarely, if ever, are the published guidelines on cancer pain, antiemesis, cancer- and chemotherapy-induced anemia, cancer-related fatigue, distress management, myeloid growth factors, palliative care, prevention and treatment of cancer-related infections, or venous thromboembolic disease shown at our weekly Tumor Board, nor has the Board ever referred to the NCCN Guidelines for Senior Adult Oncology.

Another factor described earlier is that many adult-treating oncologists are uncomfortable dealing with the challenges faced by AYAs. Psychosocial and support services for AYAs must be broader in scope and intensity than those for younger and older patients because of the many financial, emotional, developmental, and social changes and transitions that occur during this stage of life.

What really could be helpful is a patient-centered version of the NCCN Guidelines for AYAO, analogous to the professional NCCN Guidelines for Senior Adult Oncology but specifically developed for the AYAs and their families, as NCCN has developed for several cancer sites (eg, breast, colon, prostate, lung, and ovarian).12 Given the age group and the propensity for these individuals to engage each other via social media, and given the success of the LIVESTRONG Young Adult Alliance in creating a forum for AYAs with cancer to raise awareness of and disseminate these documents,13 a patient version is likely to be more successful among AYAs than in other age groups.

**ALL**

Table 1 also provides 2009 data for ALL analogous to that of all cancers. More than 1000 cases were diagnosed and 370 deaths were attributed to ALL in 2009 among 15- to 39-years-olds. A quarter of all deaths from ALL occurred during this age span. The ratio of death rate to incidence in the age group was 0.37, indicating that 4 in every 10 cases did not survive, consistent with the 49% 5-year survival rate reported for 4345 Americans in this age group diagnosed during 2000 through 2007.11 In contrast to all cancers, ALL in AYAs occurs in more males than females; the male:female incidence ratio is 1.6. In AYAs, males also have a worse prognosis than females, accounting for two-thirds of the deaths from ALL in the age group. Among males of all ages, more than 30% of all deaths from ALL occur in AYAs (Table 1).1

By themselves, these facts justify NCCN’s development and release of guidelines for the management of ALL. To add to the need, sufficient evidence shows that use of a pediatric type of treatment rather than a regimen derived from prior studies in adult patients can significantly improve the outcome data.14 Hence, the opening recommendation in the NCCN Guidelines for ALL (Figure 3B) is to either use a pediatric-inspired regimen or place the patient on a clinical trial, which is likely to also have a basis in pediatric-type therapy.

ALL also illustrates the need for collaboration between pediatric and adult oncologists. The pediatric regimens are more complex than any adult treatment regimen, because they have been developed for more than 60 years and consist of more than 100 clinical trials conducted in North America, Europe,
Australia, New Zealand, and Asia by multiple organizations. Pediatric oncologists and their treatment teams have had to assist their adult-treating colleagues in learning how to apply the regimens. Pediatric oncologists chaired the NCCN AYAO Panel, co-chaired the NCCN ALL Panel, and constituted several members of both panels. The ALL guidelines can facilitate this process of collaboration, especially when used in combination with the NCCN Guidelines for AYAO.

Conclusions

Although how widely the NCCN Guidelines for AYAO will be applied remains to be determined, they are timely, comprehensive, responsive to the AYAO PRG recommendations, and, as a good first edition, a valuable resource for medical oncologists, hematologists, gynecologic oncologists, oncologic surgeons, and pediatric oncologists who care for patients between 15 and 40 years of age. Their use will test the functionality, feasibility, and value of the algorithms and recommendations and allow early improvement of future editions. Disease-specific guidelines currently available from NCCN will be able to refer to the AYAO guidelines for those cancers that occur in AYAs. A patient version may be even more effective in encouraging adoption of the medical version by professionals, and will likely have more impact than other patient guidelines provided by NCCN. NCCN is to be congratulated on tackling the tedious task of achieving consensus in creating the first set of specific recommendations to improve the quality of care of a dynamic, diverse, disparate, difficult, demanding, and deserving patient population.

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References