The Adolescence of Young Adult Oncology

Karen Albritton, a Ronald Barr, b and Archie Bleyer c

The clinical care of young adults with cancer, and related research, was a novel focus of oncology a decade ago, but 10 years of data on patients’ needs and outcome disparities, well-reviewed in the articles of this special issue and its predecessor (June 2009), prove the merit of this subspecialty. The field, emerging from its childhood and entering adolescence, must continue to look to the future to solidify its worth. In this concluding article we examine important themes that must receive attention for the discipline to develop and flourish. We must overcome the challenges inherent in serving a population that is difficult to define, and which crosses traditional boundaries and disciplines. The field must strengthen its research in clinical trials and comparative outcomes, and must articulate the key competencies that distinguish a practitioner of young adult oncology (both to define clinical programs and educational curricula). Key opportunities are collaborations with leaders in oncofertility, developmental psychology, and transitional care, and with patient advocates. We must garner support from federal entities, as well as philanthropic agencies and accrediting bodies. With strategic effort, the field of young adult oncology will mature and grow wise.

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The articles in this issue of Seminars in Oncology and that of June 2009 have chronicled the remarkable progress for young adults (ages 20 to 39 years) within the novel discipline of adolescent and young adult (AYA) oncology, which may now be beyond its childhood and into puberty. At such a point in time, it is instructive to reflect on the teleological issues—why did this field emerge and is it destined to persevere and flourish? Any new field starts simply in response to a distinctive need, and grows when expertise is required to meet the need. We submit that AYA oncology emerged to address many of the needs expressed by AYA cancer patients (Figure 1) 1,2 and that the future of the field depends on us continuing to identify distinctive needs and to provide the interventions and proficiencies that address them.

Two other recently recognized subspecialties in oncology are a few years more mature than AYA oncology and provide informative parallels. 3 Palliative care was slow to be embraced by many oncologists, who felt they had adequate experience in managing pain and death. 5,5 Who needed an “expert” to tell them how to give morphine to a dying patient in pain? It turns out that cancer patients had needs many oncologists did not have the time or skill to uncover, and most now believe in the benefit of the palliative care given to patients by someone with expertise and focus. 6 Geriatric oncology was established to meet the unique needs of a population that is growing exponentially in number, and one that had been irrefutably underserved (with low rates of treatment and clinical trial enrollment). 7–9 By using geriatric assessments, patients are matched to appropriate management, and outcomes improve. 10,11

The notion of AYA oncology grew out of the clinical perception that adolescents and young adults experienced distinct delays in diagnosis, psychosocial hardship, and poor adherence to treatment. The concept of dedicated care in a separate physical unit was proposed as a solution to these apparent problems. The first AYA units (in New York state 12 and in the United Kingdom 13) were started to meet what were felt to be distinct—mainly psychosocial—needs. Recently, a national survey returned by 1,088 AYA cancer patients and survivors (Figure 1; see also Zebrack et al in this issue) validated these perceptions, as respondents articulated significant distinct needs and deficits in meeting them. 1,2 The array of needs reported (Figure 1, left panel) spanned the gamut from basic information about the cancer to nutritional and exercise recom-
recommendations to adoption services, family counseling, child care, and transportation. The survey indicated that most of the needs regarding nutrition, physical activity, fertility, family support, and other activities of daily living were not being met (Figure 1, right panel).

These perceptions and information on the needs of a unique population have been elaborated further by demographic and outcome data that captured the attention of the National Cancer Institute (NCI) and corresponding bodies in the United Kingdom and Australia. The primary data, outlined in the first article of this series, tell us that the population is distinct in several undeniable ways. No visual image conveys this better than Figure 2, which in various forms has become the

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**Figure 1.** Needs identified via an online survey completed by 1,089 AYA cancer patients and survivors in the United States and Canada, of which 217 respondents were in active treatment (patients) and 879 had completed therapy (survivors). The mean (range) ages of the respondents on treatment and after treatment was 31.3 (18–39) and 29.7 (18–39) years, respectively. Unmet needs refers to needs which, as of the time of survey, were not resolved. The figure combines the data for patients and survivors in the original reports.

**Figure 2.** Average annual percent change (AAPC) in 5-year relative survival rate as function of age at diagnosis, in 5-year intervals, for all invasive cancer; Surveillance, Epidemiology and End Results-9 (SEER9) data. Modified with permission from Hampton. Copyright 2005 American Medical Association. All rights reserved.
In retrospect, however, the deficit in progress among AYA patients was in part due to the HIV/AIDS epidemic and the dramatic increase in AIDS-associated cancers in males, particularly Kaposi sarcoma and non-Hodgkin lymphoma between 1982 and the mid 1990s, that along with the morbidity of AIDS had poor survival rates (Figure 3). This obscured the true progress, or lack thereof, in the AYA age range, as well as explained the negative value observed in the original data (Figure 2). When Kaposi sarcoma and non-Hodgkin lymphoma are removed, the negative values disappear and when single years of age are assessed, the AYA deficit is not as marked but nonetheless persists (Figure 4). The relative lack of progress not only persists among young adults, it is apparent in adolescents from age 13 up (Figure 4, upper panel) and thereby will require continued attention by pediatric oncologists and their teams.

When data from the most recent evaluable era, 1988–2001, are assessed, again without AIDS-related cancers, the AYA deficit not only continues, but for 12- to 30-year-olds, appears to be greater (Figure 4, lower chart) than for the entire interval since 1975 (Figure 4, upper chart). When progress is evaluated by absolute increases, the deficit is qualitatively similar from 1976–1985 to 1986–1995 and from 1986–1995 to 1996–2005 (Figure 5). Quantitatively, however, 25- to 39-year-olds have had more progress during the past two decades than the preceding two decades. In contrast, 15- to 24-year-olds had less progress during the most recent era than the prior one (Figure 5).

Another deficit that has been previously recognized is the relative lack of accrual to clinical trials among AYA cancer patients, as assessed for either the absolute number of accruals or the estimated proportion of patients in each age group accrued to national treatment trials (Figure 6).

These additional correlations supplement the original observation of the deficit into which the AYA population falls. When combined with gaps in healthcare delivery and quality of life, there should be little doubt that this population has special needs requiring attention.

So what questions in AYA oncology remain? Are we likely to answer them definitively soon? Will this knowledge be disseminated and change the practice of pediatric and medical oncologists? Will greater understanding obviate the need for specialists or increase it? Is the ongoing study of young adults with cancer worthy of a “discipline” and is the care of young adults with cancer worthy of dedicated service models? We believe that the following themes, many of which have been addressed in one or more articles in this issue of...

Figure 3. Incidence (upper charts) and 5-year relative survival (lower charts) of patients diagnosed with Kaposi sarcoma (left diagrams) or non-Hodgkin lymphoma at 15–39 years of age as function of calendar year of diagnosis, 1975–2005, SEER9.
Seminars in Oncology and its predecessor (June 2009), are the most important in the coming decade for AYA oncology:

1. Elucidation of parameters other than age that define the AYA patient
2. Development of clinical trials benefiting AYA patients
3. Specialization of health services delivery
4. Focus on oncofertility
5. Professional training in AYA oncology
6. Application of developmental behavior theory to understanding the experience of cancer in young adulthood
7. Support and utilization of the peer advocacy community

**DEFINITION OF THE AYA PATIENT (age vs other parameters)**

Who is an AYA patient? It is questionable if another decade will close the debate. Many have used convention to define the field by the population served (rather than the issues), and to define the population by age parameters. Although age does not correlate perfectly with physiologic development, developmental maturity, or tumor biology, it is the handiest and most objective variable available. The British initially targeted those aged 15–24 years as “teens and young adults (TYA)” because their hospitals excluded patients older than 14 from pediatric facilities. The NCI Progress Review Group defined AYA as those aged 15–39 years, based on the apparent lack of survival improvement and demonstrable poor clinical trial par-

**Figure 4.** Average annual percent change (AAPC) in 5-year relative survival rate as function of individual years of age at diagnosis for all invasive cancer except Kaposi sarcoma and non-Hodgkin lymphoma, SEER9. The AYA age range from 15–39 years is shaded. Upper panel, 1975–2001: A precipitous drop in survival at age 13 is apparent. Lower panel, 1988–2001: The most recent evaluable era demonstrates continued lack of progress in patient between the ages of 12–30.
participation (Figures 2–6) but also on hypotheses of host physiology (menarche to menopause),\textsuperscript{17} tumor biology, and extrapolation of social theory (the prolonging of the transition to adulthood, ie, emerging adulthood). Geriatric oncology has successfully found parameters to define patients other than chronologic age.\textsuperscript{19} It would be helpful to explore a range of hypothetical delineations for AYA patients with cancer in the coming years.

Pediatric oncology previously lumped a population with a relatively distinct outcome, children under 1 year of age with acute lymphoblastic leukemia (ALL), under the moniker “infant ALL.” Now we know that age was only a surrogate for the presence of the mixed-lineage leukemia (\textit{MLL}) gene rearrangement in 80%–90% of that age population.\textsuperscript{20} Likewise, by focused examination of the AYA population, it is likely that we will find better markers than chronologic age for their distinct outcomes. We should seek understanding of the hormonal and pharmacokinetic parameters of the host, biologic definitions of the tumors, and characterization of the developmental stages that influence quality-of-life issues. In these issues of \textit{Seminars in Oncology}, we have discussed of the biologic distinctions in young adults of ALL (distinct clinical features, cytogenetics, immunophenotype, and drug sensitivity), breast cancer (“triple negative”—especially in young black women, basal molecular subtype, increased incidence

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\caption{Accrual to National Cancer Institute Cancer Therapy Evaluation Program treatment trials by age at entry, 2001–2006. The black bars depict the absolute number of patients entered and the gray bars the estimated proportion of patients in each age group that were entered onto treatment trials. Data kindly provided by Shanda Finnigan and Steve Friedman, Cancer Therapy Evaluation Program, National Cancer Institute.}
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of lymphovascular invasion, and a distinct gene set
signature), ovarian cancer (increased incidence of epi-
thelial cancer and a less aggressive clinical course),
and sarcoma (especially gastrointestinal stromal tumors,
within the spectrum of which KIT mutation–negative
tumors predominate in children but are rare in adults).
The other expanding knowledge base that will contrib-
ute to the discussion are data on the ability of the
young adults to tolerate the aggressive treatment regi-
mens developed for children: it appears that thera-
petic regimens for ALL are tolerable at least up to the age
of 40 in most patients, further supporting the inclu-
sion of patients with “30- to 40-year-old” physiologies
in AYA studies.

CLINICAL TRIALS

The median age of subjects treated on adult oncology
protocols is between 50 and 60 years (http://www.
cancer.gov/clinicaltrials/facts-and-figures/page2); trials
are designed aptly to be tolerated by middle-aged physi-
ologies. Just as this design focus has limited enrollment
of the elderly in the past, improved only recently with
development of protocols specifically for geriatric on-
cology, we may need to create protocols targeted to
younger, healthier patients. Trial eligibility may be de-
flned initially by age (such as the risk-stratiﬁed ALL or
neuroblastoma trials), but as we learn more about
pharmacokinetic issues and host biology, they may be
better delineated by physiologic parameters such as the
patient’s hormonal status or renal function. Perhaps an
even more appealing approach in this day of limited
federal funding (and therefore limited number of trials)
is the use of study designs that individualize thera-
petic intensity according to patient characteristics (age or
host physiology). Successful examples are the ALL trials
that adjust methotrexate and mercaptopurine dosing to
white blood cell count nadir. Soliman et al suggest
that a similar dose adjustment for patients with Ewing sarcoma may remove the gap in survival outcome for
AYA males. The barriers to realization of age-unre-
stricted trials are both scientiﬁc—determining what
parameters for what disease—and cultural—the elimi-
nation of age barriers will require the collaboration of
pediatric and medical oncologists in the development,
not just in the implementation, of such trials.

The trend in treatment trial accruals for AYA pa-
tients is favorable. Since 2002, progress in increasing
the clinical trial activity of 15- to 29-year-olds with
cancer in the United States has been noted, as indicated
by the number of accruals, the proportion of patients
in the age group on clinical trials, and their proportion
of all clinical trial accruals of all ages (Figure 7). This

![Figure 7](image_url)

Figure 7. Age 15- to 29-year-old cancer patients entered on US national treatment trials by calendar year of accrual, 1997–2006. Data kindly provided by Shanda Finnigan and Steve Friedman, Cancer Therapy Evaluation Program, National Cancer Institute. (Upper panel) Absolute number of AYA patients accrued; average was 1,032 for 1996–2001 and 1,792 for 2001–2006. (Middle panel) AYA patients on treatment trials as proportion of all patients of all ages; average was 4.2% for 1996–2001 and 6.5% for 2001–2006. (Lower panel) AYA patients on treatment trials as proportion of all estimated AYA new cases; average was 5.2% for 1996–2001 and 8.2% for 2001–2006.
trend is more favorable when compared to younger and older patients in whom a decline in accruals and accrual proportion has been noted during the same interval.\textsuperscript{20} Most of the accrual increase was in phase III studies of leukemia and lymphoma, for which the national mortality rate did decline during the years of increased accrual.\textsuperscript{26}

**HEALTH SERVICES DELIVERY**

The best way to ensure the viability of the field of AYA oncology is to demonstrate improved outcomes, preferably with a profit margin. A reasonable criticism, predominantly from the busy community of medical oncology, is that dedicated units with comfortable snazzy furniture, and modern multi-media and technology equipment, or dedicated providers who have extra training and take time to address psychosocial issues, are valuable resources for patients of all ages. Funds for such amenities just for AYA patients cannot be mandated to come from global operating budgets unless there is indisputable evidence that such items improve outcomes. Our tasks are several:

1. To prove outcome differentials, and determine what elements of care make the difference. Although we have good evidence that AYAs treated on pediatric regimens for ALL do better than on adult protocols, we have a limited understanding of which elements provide the survival advantage. If the difference is merely the chemotherapeutic regimen, the current adult cooperative group trial (C10403) should have equal outcomes to the Children’s Oncology Group (COG AALL0232) trial. If not, what is the role of provider and institutional experience, or of supportive care? It is very possible that we will find AYA patients with other diagnoses who have improved survival when treated by medical oncologists rather than pediatric oncologists (e.g. metastatic germ cell tumors or melanoma) and we will have to examine what factors are influencing that differential outcome.

2. As a corollary to the first task, to identify outcomes other than survival that also have quantifiable value. In AYA oncology this could include objective measures such as impact on work and schooling, incidence of physical limitations, infertility, depression and suicide, late effects and second malignancies, divorce, mental health in family members (including spouses, parents, and children of young adults), and patient-reported outcomes including quality of life, self-efficacy, social competence, sexual functioning, stress, satisfaction, and symptoms (e.g. nausea, fatigue, anxiety). Patient-reported outcomes (PROs) are gathering weight as important and legitimate metrics, and it is recognized that they need to be studied and validated in specific populations\textsuperscript{27}; it is likely that the AYA population is such a unique population. The Lance Armstrong Foundation funded three grants in 2008 to establish appropriate tools to measure quality of life in AYA cancer patients.

3. Garnering philanthropic support that will supplement federal and institutional funds. In most cases private donors are more willing than governmental agencies or individual institutions to support care enhancements (including physical environment and psychosocial support) before definitive evidence is achieved. The Teenage Cancer Trust in the United Kingdom and Canteen in Australia are established foundations with name recognition for the AYA cause. They, and other private organizations, have funded a variety of interventions and supports for AYAs. Of course, we must be good stewards of such philanthropy by monitoring the supported interventions and “proving” their worth; little has been published evaluating these measures to date.\textsuperscript{28}

4. Considering and capitalizing on local economic opportunities. An institute’s AYA program can provide market differentiation. This could be particularly appealing to pediatric centers, for whom raising upper age limits (e.g., to 25 years) to include the AYA population is a new market expansion even in the absence of competitors. For adult centers, an AYA program could attract patients otherwise going to local competition. One tactic is to consider a broader strategy that includes care of AYAs with diseases other than cancer. Several other specialties struggle with transition of their aging pediatric patients with chronic conditions, for example, cardiology (congenital heart disease\textsuperscript{29}), hematology (sickle cell disease\textsuperscript{30} and hemophilia), pulmonology (cystic fibrosis\textsuperscript{31} and asthma), nephrology (chronic dialysis\textsuperscript{32,33}), and rheumatology (chronic arthritis\textsuperscript{34}). There is a growing call from organized medicine to attend to transition\textsuperscript{35} and for increasing research and clinical practice addressing appropriate approaches to transition,\textsuperscript{36,37} including transition of AYA cancer patients.\textsuperscript{38,39} Many resources at an institution—developmental specialists, dedicated AYA units, vocational and insurance resources, psychologists—could serve common goals in transition and AYA oncology.

**ONCOFERTILITY**

The AYA oncology community would benefit greatly from embracing oncofertility under its purview. Oncofertility is a new term, developed by the recipients of one of the National Institutes of Health (NIH) Roadmap Initiatives, for the field of fertility in cancer patients.\textsuperscript{40}
At institutions trying to establish and grow an AYA program, oncofertility can be a wedge issue that is decidedly AYA specific and undeniably “value added.” Clearly it is a concern that will have a bell-shaped curve of importance to the population of 15- to 40-year-old cancer patients. It has both medical and psychological components. If an oncologist can access expert and dedicated services in one phone call, and increase patient satisfaction and decrease late effects, the value of an AYA service is tangible. A cancer center that offers fertility preservation services conveys to patients that there is an anticipation of cure, that value is placed on the quality of their survivorship, and that state-of-the-art technology is available to achieve survivorship. The American Society of Clinical Oncology (ASCO) published guidelines recommending that oncologists should “address the possibility of infertility with patients treated during their reproductive years and be prepared to discuss possible fertility preservation options or refer appropriate and interested patients to reproductive specialists.” However, many oncologists lack comfort, time, or competence to navigate discussions of fertility preservation with the young adult patient. Having a nurse educator (teamed with staff from urology, gynecology, andrology, reproductive endocrinology, psychology, and ethics) provide education, decision-making guidance, and facilitation can be a concrete and nonthreatening “early win” to validate a dedicated AYA service.

TRAINING

If we conclude that expertise in and focus on this population improves outcomes, how are we to train the providers who deliver this advantage? What are the essential competencies? Should there be standardized training or certification for physicians? For a subspecialty to gain formal recognition there must be certified and accredited training that is accepted by the professional bodies in organized medicine. It is unclear if there is one path or multiple acceptable paths to clinical expertise as an “AYA oncologist.”

Again we can examine the experience of the fields of palliative care and geriatric oncology. Palliative care is a certified subspecialty pursued through a 1-year clinical fellowship after board certification in internal medicine, pediatrics, or several other specialties. Initially the certification was given by the American Board of Hospice and Palliative Medicine, but after 10 years, Hospice and Palliative Medicine was accepted as a subspecialty by the American Board of Medical Specialties (ABMS) and the training programs were accredited by the Accreditation Council of Graduate Medical Education (ACGME). It is possible that a 1-year clinical fellowship in AYA oncology could be designed for individuals boarded in either pediatric or medical oncology. Appropriate curricula and testing could be designed and overseen initially by a Board of AYA Oncology, with the hope of formal accreditation in the future.

Geriatric medicine has provided fellowship training for nearly 40 years, and programs have been accredited and Added Qualification in Geriatrics (AQG) certificates given by the American Board of Internal Medicine (ABIM) for 20 years. A unique partnership between ASCO and the Hartford Foundation for Aging funded 10 institutions in 2006 to combine oncology and geriatric training in a single track that provides ABIM recognized board certification in medical oncology and geriatrics in 36 months; however, the success and utilization of this track have yet to be proven. Although a similar joint fellowship in adolescent medicine and pediatric or medical oncology could be conceived, it is not clear that the training in medical or pediatric oncology alone provides expertise in the management of all of the tumors seen in the AYA population, nor that adolescent medicine completely covers the issues of patients between 25–40 years of age.

Even if a certification is developed in AYA oncology, only a minority of cancer patients age 15–40 years will be cared for by individuals with such specialty training, just as it is acknowledged that a minority of elderly cancer patients will be cared for by providers board-certified in geriatric oncology. Besides developing a core of academic expertise at a few centers, specialty training of focused individuals, we must integrate key AYA oncology topics into the general education of pediatric and medical oncologists. The “standards” committee of the Lance Armstrong Foundation LiveStrong Alliance is responding to one of the recommendations of the NCI AYA Oncology Progress Review Group in developing such a list of competencies, recommended to be integrated into the training of oncology fellows, nurses, psychologists and other providers as well. The online postgraduate certification course offered by Coventry University in England is an attempt to formalize such a curriculum.

DEVELOPMENTAL THEORY AND PSYCHOSOCIAL IMPACT OF CANCER

As pointed out by Eiser and colleagues, we have much to learn about the impact of cancer on the young adult’s psychosocial health and quality of life. There are more than 60,000 young adults between 20 and 40 years of age who are told each year in the United States that they have “the big C.” Whether their prognosis is good or poor, they have a profound brush with mortality, and most have a large and sometimes permanent interruption in their daily routine, opportunities, and goals. Life span developmental theory holds that psychological maturation is a lifelong process. A life event as significant as cancer is clearly going to be processed differently depending on the life stage at...
which it is experienced. The issues of maintenance of identity, self-image, sexuality, normalcy, and avoidance of isolation are all developmentally specific to this age range. We need to understand both the impact of cancer on normal development and the impact of developmental stage on the experience of cancer. The field of AYA oncology should engage experts in developmental psychology, behavior, and sociology, including those studying “emerging adulthood” a “new” phase of the life cycle, roughly between 18–30 years, described as a protracted time of identity development and egocentrism.\(^4^9\)\(^5^0\) Using developmental psychology theory, we can develop appropriate instruments to measure quality-of-life and design interventions to minimize the negative impact (and maximize the positive impact) of cancer and its treatment in young people.

**PEER SUPPORT AND ADVOCACY**

For the discipline of AYA oncology to be sustained, particularly in tight economic times, we will benefit greatly from the work and support of the constituency of young adult cancer patients. Survivors of AYA cancer can both provide voluntary but expert peer-to-peer support, and the energy and passion needed for institutional or federal policy improvement. Peer support—especially in the age of media social networking—is listed frequently as a top need of AYA patients.\(^5^1\) No one says “I get it” like someone who’s got it (or had it), especially to skeptical and socially oriented young adults. Peer navigation and guidance for young adults is particularly important because of their naïveté of the healthcare system, frequent lack of self-confidence, and often limited social support, and the extra challenges posed by navigating a healthcare system not designed to care for this age group.\(^5^2\)

Beyond providing peer support, AYA advocates can be a force for moving the field of AYA oncology forward, raising money for research, improving clinical practice, increasing awareness, and promoting policy change. Young survivors make energetic, passionate, idealistic advocates, especially those post-college and pre-parenting who have the time and energy to devote to advocacy tasks; many say it is an important part of their healing. Harnessing and sustaining their energy can be difficult, as young adults have busy lives and are not always looking for a long-term commitment, but several successful young adult advocacy organizations have been founded and/or staffed by young adult cancer survivors (Planet Cancer,\(^5^3\) Ulman Fund for Young Adults,\(^5^4\) SAM Fund,\(^5^5\) Young Adult Cancer Canada [formerly RealTime Cancer],\(^5^6\) and I2Y\(^5^7\)). Unlike childhood cancer foundations, often started or run by parents, or large cancer advocacy organizations, or advocacy organizations for rarer adult cancers (often run by bereaved families), these advocacy groups have a gritty realism that comes from the involvement and experience of the young adult survivor. The LiveStrong Young Adult Alliance\(^5^8\) is an organization of organizations that seeks to bring together the AYA advocacy groups to develop an overarching strategy to influence change.

**CONCLUSIONS**

We predict that the field of AYA oncology will grow and flourish, based on its scientific merit and medical usefulness for patients and families. As once described for palliative care and geriatric oncology, the tasks for AYA oncology will have to include

> “staking out and promoting a special area of knowledge, conducting research to further develop that knowledge base, finding ways to support the clinical practice of the discipline, training others in the practice of the field (often fighting for access to the curriculum), and developing the social mechanisms for these functions, including the gatekeeping role, professional organizations, journals, fellowships, and specialty or board certification exams.”\(^5^3\)

With strategic planning, collaboration, and monitoring of metrics of success, and attention to these important themes and challenges and opportunities, the research and care of young adults with cancer is destined to reach its own middle age.

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