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Editorial

Adolescents and Young Adults With a "Rare" Cancer: Getting Past Semantics to Optimal Care for Patients With Germ Cell Tumors

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Introduction

Germ cell tumors (GCTs) are the third most common cancer diagnosis in adolescent and young adult (AYA) patients aged 15–24 years [1]. Many cancers that arise in AYA patients, including GCTs, are defined as "rare" because they are relatively infrequent during early childhood and older adulthood [2]. Consequently, the clinical care, clinical trials, and biological study of these cancers have not progressed synchronously with common childhood or adult cancers, and gains in overall survival (OS) for this age group are only half those in either younger or older patients [3]. We reflect on how to address this lack of progress, using as our lens our own experience in creating an international, cross-disciplinary remodeling of the clinical trial development for GCTs to overcome the barriers created by the structure of conventional medical practice.

Reframing the Meaning of "Rare"

GCTs constitute only 4% of all pediatric cancer cases diagnosed annually but rank as the third most common AYA cancer after lymphoma and carcinomas and account for up to 20% of cancer in the male AYA population [4–7]. However, the clinical care for GCTs in AYAs is divided between multiple medical and surgical disciplines (pediatric oncology, gynecology, urology, and medical oncology), and each discipline continues to recognize GCTs as a minor component of their practice. If one were to use neither an adult nor a pediatric frame but rather an AYA frame of patients aged 15–24 years, rare cancers such as GCT would be described as "common" and many common cancers of pediatrics or adulthood would be rare.

Redefining Overall Survival

Because more than 90% of patients treated for a GCT are cured, the quality of survival becomes increasingly important for this group of young patients [8]. Five- or even 10-year survival may not be synonymous with normal life expectancy. Travis et al. have shown that a 20-year old young man, cured of his testicular (GCT) cancer, faces a >50% chance of developing a second malignant neoplasm by age 75, nearly doubling his standard lifetime risk of 26% of developing cancer [9, 10]. Woodward et al. reported a twofold risk of cardiovascular disease among testicular cancer survivors [11]. Cisplatin, a key component of the standard chemotherapy treatment for GCT, is measurable in the serum years after exposure: at autopsy, cisplatin has been detected in every organ of the body [12–15]. Furthermore, cisplatin has been shown to be mutagenic and is considered a human carcinogen [16–19].

Serum levels of cisplatin measured 10 years after testicular cancer treatment predict the severity of persistent neuro- and ototoxicity [20]. We cannot be complacent that we have defined the optimal therapy in the face of such significant late effects of standard therapy.

Re-Emphasizing the Importance of Recruitment of AYAs to Clinical Trials

Abundant evidence suggests that health care systems that are active in research have better health outcomes because of the introduction of state-of-the-art and standardized care approaches [21–23]. Ferrari et al. have recommended that the

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inclusion of cancer patients in clinical trials be a benchmark of the optimal standard of care [24]. In both the U.K. and the U.S., low recruitment to clinical trials has been documented for AYA patients, with 2.5% and 13.8% of patients aged 15–19 years in the U.K. the U.S., respectively, and falling to 10.6% of U.K. patients aged 20–24 years and 4.6% of U.S. patients 20–29 years enrolled in a clinical trial [25, 26].

Bleyer et al. described multifactorial reasons for poor recruitment of AYA patients to clinical trials [27]. Some barriers to participation include inadequate trial design, failure to open trials for perceived rare tumors in all centers, and a paucity of age-directed information about trials; however, the authors noted that AYAs have shown willingness to participate when clinical trials are available [28, 29]. Another important factor may be referral pathways: the National Cancer Intelligence Network England reported that 50% of AYA patients with a gonadal GCT were not referred into a specialist AYA service [30].

Redefining "Rare" in Terms of Clinical Trial Design

The International Germ Cell Consensus Group (IGCCG) devised an algorithm to predict overall survival based on risk assessment at diagnosis. Good risk patients have an expected OS of >90%, but poor risk patients can expect an OS of <50% [31]. In the U.S. in 2014, 8,820 men are projected to be diagnosed with testicular cancer [32, 33]. Using data from SEER18, which includes data on site of metastasis and diagnostic alpha-fetoprotein levels, we estimated that there are approximately 370 new poor-risk testicular cancer patients per year in the U.S. [34]. Under the auspices of multi-institutional national clinical trial organizations such as the Children's Oncology Group (COG) in the U.S. and Canada and the Children's Cancer and Leukemia Group in the U.K., randomized clinical trials of diseases with far fewer than 500 incident cases per year have been successfully conducted. When national sample size has been insufficient, international collaborations have been organized, such as the osteosarcoma EURAMOS trial [35]. However, adult clinical trials conducted over the last decade aiming to identify a regimen with superior outcomes to bleomycin, etoposide, and cisplatin (BEP) chemotherapy in men with IGCCC poor-risk testis cancer have either failed to achieve sufficient accrual to provide statistically meaningful results (e.g., paclitaxel-BEP [36]) or have not been able to progress from an informative, positive phase II trial to a definitive phase III trial because of a lack of conviction within the testicular cancer community that it would be possible to enroll sufficient number of patients (e.g., carboplatin, bleomycin, vincristine, and cisplatin followed by BEP [37]; accelerated BEP [38, 39]). A recent exception, the GETUG 13 trial [40], showed that an intensified approach in poor-risk patients who had inadequate tumor marker decline was superior to standard BEP; however, this trial took 9 years to accrue the 260 patients required to answer the study question. We suggest that designing GCT trials based on expected outcome rather than age and gender would allow the GCT community to answer the common outstanding questions around optimization of therapy more efficiently. We contend that it is time to move beyond trial eligibility that is defined only by which clinical trial organization can "lay claim" to the patient.

Solution: Recognition That Optimal Care of AYA Patients Requires a New Structure and Language Within Oncology

The approach to AYA cancer care started to change with the recognition of the specific medical and psychological needs of AYA patients. Philanthropic organizations have been at the vanguard of this advocacy. In the U.K., the mission statement of the Teenage Cancer Trust is "We exist to improve the quality of life and chances of survival for the six young people aged between 13 and 24 diagnosed with cancer every day in the UK. We want to make sure every one of them has access to the best possible care and professional support from the point of diagnosis [41]." An analogous sister organization, Teen Cancer America, has recently been founded in the U.S. In its landmark publication, "Improving Outcomes: Guidance for Children and Young People with Cancer," the National Institute for Clinical Excellence, which provides clinical practice and quality guidelines to the National Health Service in the U.K., has decreed that AYA-appropriate services must be provided to every AYA cancer patient [42]. Consequently, well-established national referral pathways have been developed for AYA patients to ensure access to cancer care in specialist AYA treatment centers. Teenage Cancer Trust has supported the development of 27 AYA centers within the U.K. to ensure this goal is achieved.

Besides physical infrastructure, Teenage Cancer Trust and other AYA cancer charities, such as the Katie Walker Cancer Trust (U.K.) and the Bridging the Gap Fund (U.S.), have invested in the intellectual capital required to advance the field. With support from these organizations, the Malignant Germ Cell International Collaborative (MaGIC) brought together U.S. and U.K. national experts in pediatric GCTs who agreed to merge deidentified clinical trial data spanning 25 years of platinum-based therapy to develop a more nuanced risk stratification system that could serve as the basis for future collaborative pediatric clinical trials in GCTs, analogous to the IGCCC. This collaboration intentionally included pediatric oncologists, pathologists, surgeons, statisticians, and basic scientists. The resultant risk stratification overturns previously understood risk factors and prognostication and serves as the basis for the new, jointly designed UK-COG clinical trial (J. Nicholson, C. Rodriguez-Galindo, H. Dang et al., manuscript in preparation).

The more challenging frontier in GCTs was to extend knowledge beyond the artificial barriers of age and gender. MaGIC has successfully engaged the National Cancer Research Institute Testis Clinical Study Group and the US Gynecologic Oncology Group. Investigators from these organizations have contributed their respective AYA clinical trial data to extend risk prognostication from early adolescence through young adulthood. Pivotal benefits of these collaborations will be the ability to carry out correlative translational studies that span age and gender. Of note, the recent collaborative formed between COG and SWOG cites MaGIC as an example of good practice (personal communication, D. Freyer) [43].

Conclusion

For AYA patients with GCTs, AYA units provide the physical setting. The MaGIC model offers a successful template of collaboration to create those age-appropriate clinical trials.

The joint clinical trial under development by adult and pediatric cooperative groups in the U.S. and the U.K. will offer AYA patients who are diagnosed with GCTs the opportunity to benefit from centralized expertise in a tumor type that is more common in their age group than at any other time during life. In rare cancers, for which small patient numbers preclude statistically meaningful results in a single country, much less a single institution, targeted philanthropic funding to support cross-disciplinary and international work has provided the necessary "magic" to catalyze the first steps in knowledge expansion. Our recommendation is that cancer organizations, both governmental and charitable, continue to fund this approach for rare AYA tumors. A framework that spans age and gender will provide the scaffolding for a more robust approach to the management of diseases historically splintered by our academic oncologic semantics.

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For Further Reading:

Stephen B. Riggs, Earl F. Burgess, Kris E. Gaston et al. Postchemotherapy Surgery for Germ Cell Tumors—What Have We Learned in 35 Years? ***The Oncologist*** 2014;19:498–506.

Implications for Practice:

Patients with advanced testicular cancer will often be considered for surgical consolidation following chemotherapy. This review article focuses on the evaluation and role of surgery in treatment of these complex patients. It underscores the selection of patients, vital role of surgery, as well as providing guidance in the use of surveillance as opposed to surgical extirpation.