ACTA SCIENTIFIC CANCER BIOLOGY

Volume 3 Issue 1 January 2018

Mini Review

Malignancies of Adolescents and Young Adults: Not a Child, not an Adult

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Received: November 01, 2018; **Published:** December 12, 2018

Short Review

The malignancies of Adolescents and Young Adults (AYA) represent a unique and special group of diseases with very distinct epidemiological, clinical and biological characteristics. A big difference in these characteristics exists when compared to the childhood and older adult's malignancies and thus this age group requires special approach and management.

Definition

AYA are defined as being an age group between older patients in pediatric oncology or hematology practice and the younger patients in adult practice. No clear definition till now defines the age range because of the differences concerning this cut-off among the different healthcare systems [1,2]. The World Health Organization defines adolescents as those aged 10 - 19, whereas youths as those aged 15-24 years [3]. The US Surveillance Epidemiology and End Results (SEER) program and few other international societies define the AYA cancer population as those aged between 15 and 29 years [4].

However, the 2006 Adolescent and Young Adult Oncology Progress Review Group (AYAO PRG) report uses 15-39 now the standard used by the National Cancer Institute (NCI) as well as the age range generally used by Journal of Adolescent and Young Adult Oncology [5].

Furthermore, three age cohorts can well define AYA as early young adulthood (15 - 18 years old), young adulthood (19 - 24), and late young adulthood (25 - 39); another subdivision can be useful also defining adolescents as individuals between 10-19 years and Young adults between 20-39 years. These subdivisions can account for the differential physiological and psychosocial sides experienced by AYAs within each age category. An important implication exists in the design of clinical interventions, trials and research protocols [6].

Epidemiology and classification

The incidence of AYA malignancies is around 200-300 cases per million persons.7 There is around 50% higher annual incidence comparing adolescents to younger children, and 50% higher again comparing adolescents to Young Adults [7]. An increase of 0.9% per year incidence was noticed mainly due to the increase in incidence of juvenile melanoma (5% increase), thyroid cancer (3.5%), ovarian cancer (3.0%) non-Hodgkin lymphomas (NHL, 2% increase) and germ-cell tumors (2% increase) [8]. Cancer occurring between the ages of 15 and 39 years is 4 times less rare than cancer occurring during the first 15 years of life and consists of 2% of all invasive cancer in Europe, about 66,000 patients in Europe each year. Among 15 - 24 years aged AYAs, cancer is the leading disease related cause of death and ranks third as the most significant cause of mortality in young people in Europe (10% of deaths, about 2,000 deaths annually) ranking behind road traffic injuries (46%) and suicides (24% of deaths). Whereas among those of 25-39 years, cancer ranks as the second leading cause of disease-related cause of death (13% of deaths) behind cardiovascular disease (15% of deaths) [9].

Epithelial tumors can be seen in adolescents but usually more frequent in young adults. Along with nasopharyngeal carcinomas, thyroid cancer and melanomas, they are "adult type" tumors seen in AYA. However embryonic rhabdomyosarcoma, Wilms tumors and neuroblastomas are rarely seen true "pediatric type" tumors occurring in AYA [4]. Lymphomas, leukemias, sarcomas and central nervous system (CNS) tumors are more frequent in the 15-19 years group, whereas lymphomas, melanoma, thyroid cancer and testicular cancer are more frequent in the 20-29 years group [4]. Breast and colorectal cancers are of high frequency in the 20-29 years group [4]. AYA tumors are best classified using by a pathology-driven approach and not by adult cancer classification system which is tumor primary-site specific [8]. Figure 1 shows the distri-

bution of the 12 main tumor groups in children and adolescents. Figure 2 shows the distribution of the 13 main tumor groups in older adolescents and young adults. The 2 figures clearly show the differences in incidence and proportions of tumor types among the different age groups and the AYA age continuum [5,10].

Figure 1: Types of cancer in children and adolescents (% cases/disease). (Courtesy of Pritchard-Jones K., *et al.*).

Figure 2: Types of Cancer in Older Adolescents and Young Adults (% cases/disease). (Courtesy of Progress Review Group).

Risk Factors and Genetics

The vast majority of cancers in AYA population are sporadic of unknown etiology and with a negative family history of cancer. Less than 10% of AYA malignancies are associated with genetic syndromes with an increased malignancy incidence [8]. Extremely rare environmental factors have been observed in the pathogenesis of AYA cancer such as Clear-cell adenocarcinoma of the vagina or cervix (Maternal exposure to diethylstilbestrol during pregnancy), Liver tumors (Congenital exposure to HBV/HCV), Cervical Cancer (HPV), Kaposi Sarcoma (HIV), HL and Burkitt lymphoma (EBV), Second primary tumors (childhood exposure to chemo-radiation) and Juvenile melanoma (UV sunlight exposure) [8]. Genetic syndromes that are usually associated with AYA malignancies are Neurofibromatosis (NF1 and NF2), Li-Fraumeni syndrome (TP53), Xeroderma pigmentosum (XP), Ataxia-telangiectasia (ATM), Fanconi pancytopenia, Hereditary dysplastic nevus syndrome, Turner, Beckwith-Wiedemann, Bloom and Gorlin's syndromes, Multiple Endocrine Neoplasia syndromes (MEN), BRCA1/BRCA2 tumor suppressor gene mutations, Familial Adenomatous Polyposis and Lynch syndromes [11]. The mutational rate and burden are very low in AYA in comparison with adult's malignancies that are usually associated with multiple cancer-driving mutations. The mutation specificity is usually disease-specific rather than shared. Furthermore, only 30% of significantly mutated genes overlap with adult pan-cancer analysis [11]. Although advances in sequencing techniques allow sequencing the whole exome and genome effectively, the frequency of germline mutations and their therapeutic implications are not well studied in this age category due to the rely on candidate gene approach and selected families [12].

Diagnosis, Treatment and outcome

AYA have a tendency to consider themselves as "unaffected" by serious diseases, such as cancer. Healthcare personnel and patients can easily underestimate the symptoms that should stimulate investigations such as severe fatigue, headache, enlarged lymph nodes and weight loss. Also, the demanding education, social circumstances or work-place obligations may lead AYA to neglect serious health problems. They are reluctant to report symptoms or signs especially those related to reproductive system such as amenorrhea and testicular mass causing a delayed diagnosis and progression of the disease

AYA and especially adolescents need special care and treatment by skilled personnel in appropriate infrastructure or centers. There are evidences from retrospective and cohort studies that relate an improved outcome to the treatment in specialized reference centers. Survival seems to correlate with the number of adolescents with malignancy seen annually in each center [13,14]. Approximately 75% of adolescents with cancer achieve long-term overall survival. AYA patients have fewer comorbid conditions compared with older cancer patients, and thus are usually able to tolerate intense chemotherapy and surgery with less morbidity. 5-year survival rates for the most common tumor types (CNS tumors, NHL, ALL, HL, germ-cell tumors) range from 45% to 90% [15]. An example concerning the different outcomes when using different therapeutic approaches can be given in the treatment of ALL in adolescents. "FRALLE 93" (pediatric protocol with age <20 years) was compared to "LALA 94" (adult protocol with age 15-60 years) that have treated 77 and 100 adolescents respectively. The 5-year event free survival were 67% and 41% respectively with a P value <0.0001, showing a clear benefit when using the "FRALLE 93" over "LALA 94" [16]. Retrospective analyses have shown that AYA patients with certain pediatric-type cancers, such as acute lymphoblastic leukemia (ALL) [16], rhabdomyosarcoma [17], and Ewing sarcoma [18], have superior outcomes when treated with pediatric protocols. Alternatively, there is a lack of compelling evidence that pediatric protocols improve outcomes in AYA patients with acute myeloid leukemia (AML), HL, and NHL [19,20].

The curative approach requires that treatments should be given in a "state of the art" fashion within international study protocols including: Combined modality treatment, aggressive surgical approaches, high-dose radiotherapy when indicated, dose-dense or high-dose chemotherapy with autologous marrow/stem-cell rescue in defined indications or within clinical trials, avoidance of unnecessary treatment delays or dose reductions [15].

The main reasons for the slow improvement in outcomes is that AYA patients are still not all treated in appropriate medical structures in addition to a low rate of participation in clinical trials. Other factors can play a major role also such as differences in disease biology, lack of consistency in treatment approaches, poor compliance with or intolerance of therapy, lack of health insurance, delays in diagnosis, and physician's lack of familiarity with cancer in the AYA population.

Psychological considerations

AYA often have long hospitalizations and they are under the supervision of health care providers, causing a significant isolation from their families and peer group. Isolation and alienation are common among AYA individuals diagnosed with cancer, because they often miss out on the life experiences shared by their peers [21]. Health-related unemployment is very common in young adults surviving an AYA malignancy, lower rates of health insurance coverage, and more difficulties obtaining coverage compared with their siblings. These issues seem to be significant predictors of psychological distress in the childhood cancer survivor population [22]. Reinforcing relationships with family, peers, and health professionals is an important aspect of life for AYA with cancer. Psychological support by personnel with specific communication skills (e.g. timing of key discussions, use of humor etc…) is crucial during and after the treatment. Support by physiotherapists, dentists, make-up specialists and plastic surgeons along with the support by social workers ensuring smooth re-incorporation into educational, professional and social activities are mandatory. Peer group support should continue during treatment since AYA patients can benefit from being managed together so they are 'all in the same boat' as said [23,24]. Special considerations are to be given for the adherence to treatment and keeping up with appointments to avoid delayed identification of side effects, complications, or secondary cancers.

Late toxicities and complications

The survivors from AYA malignancies are prone for late side effects related to cancer treatment. It is mainly dependent on the age at initial diagnosis and the type of treatment. They can affect every aspect of the patient's health, quality of life and psychological well-being [25]. Appropriate management of symptoms and side effects should be an integral part of the management of AYA with malignancy. Disabling surgeries can cause late effects that interfere with patient's quality of life such as mutilating surgeries in the limbs, head and neck or torso cause disfigurement and resulting in functional disabilities. This may be reduced with recent advances in limb-sparing surgery with modern endoprostheses and other techniques [15].

Treated AYA are at increased risk of developing a variety of secondary cancers compared with the general population. The risk and specific types of secondary cancers are widely dependent on the type of initial cancer diagnosis and treatment exposure [26]. Radiotherapy has been associated with an increased risk for late mortality, development of second malignancies, pulmonary, cardiac, and thyroid dysfunction, growth abnormalities and infertility [27].

Alkylating agents are associated with an increased risk of infertility in both male and female patients [28]. Anthracyclines are associated with cardiac dysfunction, whereas neurotoxic chemotherapies, such as methotrexate and cytarabine, can result in CNS dysfunction [29]. Higher cumulative doses of cisplatin, ifosfamide, or epipodophyllotoxin are associated with hearing loss, renal dysfunction, and secondary AML, respectively [30-32]. Lung injury, pulmonary fibrosis, respiratory failure is associated with the administration of bleomycin >300-360 IU. Myopathy, immunosuppression, diabetes, hypertension, osteoporosis, bone necrosis, mood disturbances are well known consequences of high doses and chronic steroids administration [33].

Evidences strongly support the importance of fertility preservation in AYA and should be an essential part in the management of their cancers. Infertility, whether chemo- or radio-induced is usually caused by Chemotherapy-associated hypogonadism, Pituitary dysfunction (Cranial irradiation) and Hypothyroidism [28]. Oophoropexy and embryo cryopreservation after in vitro fertilization (IVF) are the 2 established options for fertility preservation in women. Mature oocyte cryopreservation and ovarian tissue grafting and freezing are emerging techniques for fertility preservation in young women [28,34]. GnRH agonists have been used as ovarian protectors during chemotherapy [35]. In male patients, semen cryopreservation and transplantation of spermatogonia are the options for fertility preservation [28].

Conclusion

AYA malignancies remain a unique group of diseases that requires special diagnostic and therapeutic approaches. They are in the midway between pediatric and adult tumor epidemiology. An effort in supporting the patient and family is highly needed. Also, the improvement of the expertise is needed for state of the art management of the AYA. The goal is to always aim for cure. Undertreatment should be avoided as well as overtreatment and debilitating late toxicities. Multidisciplinary approach and management are mandatory and referral to specialized centers is obligatory whenever they exist. Psycho-social support is required and of major importance. The long-term follow up is necessary especially for the late toxicities and secondary malignancies. Prognosis is excellent for some patients; however, improvement in several gaps is still needed. The outcome is lagging behind that seen in pediatric and adult tumors. Clinical research and clinical trials are not efficient and the investigators still need to make lot of efforts.

Bibliography

1. Erikson E. "Identity, Youth and Crisis". New York Norton (1968).
2. Pollock BH, Birch JM; "Registration and classification of adolescent and young adult cancer cases". *Pediatric Blood and Cancer* 50.5 (2008): 1090-1093.
3. http://www.who.int/topics/adolescent_health/en/
4. Bleyer A., *et al*. "National Cancer Institute, NIH Pub. No 06-5767". "Cancer Epidemiology in Older Adolescents and Young Adults 15-29 Years of Age, Including SEER Incidence and Survival 1975-2000". (2006).
5. Adolescent and Young Adult Oncology Progress Review Group. "Closing the gap: research and cancer care imperatives for adolescents and young adults with cancer". (NIH Publication No. 06-6067) Bethesda, MD Department of Health and Human Services, National Institutes of Health, National Cancer Institute, and the LIVESTRONG Young Adult Alliance (2006).
6. Liebert MA. "What Should the Age Range Be for AYA Oncology?". *Journal of Adolescent and Young Adult Oncology* 1.1 (2011).
7. Ries LAG., *et al*. "SEER Cancer statistics Review". *National Cancer Institute* (2001).
8. Birch JM., *et al*. "Classification and incidence of cancers in adolescents and young adults in England 1979-1997". *The British Journal of Cancer* 87.11 (2002): 1267-1274.
9. Stark DP and Vassal G. "Tumors in Adolescents and Young Adults". *Progress in Tumor Research* 43 (2016): 1-15.
10. Pritchard-Jones K., *et al*. "Children witn cancer: Driving the global agenda". The Lancet Oncology, March 14.3 (2013.): 189-191.
11. Bandopandhayay P and Meyerson M. "Landscape of childhood tumours". Nature 555.7696 (2018): 316-317.
12. Zhang J., *et al*. "Germline mutations in predisposition genes in pediatric cancer". *New England Journal of Medicine* 373.24 (2015): 2336-2346.
13. Collette L., *et al*. "Impact of the treating institution on survival of patients with "poor prognosis" metastatic nonseminoma". European Organization for Research and treatment of Cancer Genito-Urinary Tract Cancer Collaborative Group and the Medical Research Council Testicular Cancer Working Party. *Journal of the National Cancer Institute* 91.10 (1999): 839-846.

14. Wein S., *et al*. "Role of palliative care in adolescent and young adult oncology". *Journal of Clinical Oncology* 28.32 (2010): 4819-4824.

15. Hollis R and Morgan S. "The adolescent with cancer - at the edge of no-man's land". *Lancet Oncology* 2.1 (2001): 43-48.

16. Boissel N., *et al*. "Should adolescents with acute lymphoblastic leukemia be treated as old children or young adults? Comparison of the French FRALLE-93 and LALA-94 trials". *Journal of Clinical Oncology* 21.5 (2003): 774-780.

17. Ferrari A., *et al*. "Rhabdomyosarcoma in adults. A retrospective analysis of 171 patients treated at a single institution". *Cancer* 98.3 (2003): 571-580.

18. Scurr M and Judson I. "How to treat the Ewing's family of sarcomas in adult patients". *Oncologist* 11.1 (2006): 65-72.

19. Sandlund JT. "Should adolescents with NHL be treated as old children or young adults?". *Hematology. American Society of Hematology. Education Program* (2007): 297-303.

20. Tai E., *et al*. "Differences in non-Hodgkin lymphoma survival between young adults and children". *Archives of Pediatrics and Adolescent Medicine* 164.3 (2010): 218-224.

21. Morgan S., *et al*. "Sex, drugs, and rock 'n' roll: caring for adolescents and young adults with cancer". *Journal of Clinical Oncology* 28.32 (2010): 4825-4830.

22. Zeltzer LK., *et al*. "Psychological status in childhood cancer survivors: a report from the Childhood Cancer Survivor Study". *Journal of Clinical Oncology* 27.14 (2009): 2396-2404.

23. Kelly D., *et al*. "'Being in the same boat'": ethnographic insights into an adolescent cancer unit". *International Journal of Nursing Studies* 41.8 (2004): 847-857.

24. Gibson F and Soanes L. "Long-term follow-up following childhood cancer: maximizing the contribution from nursing". *European Journal of Cancer* 37.15 (2001): 1859-1866.

25. Soliman H and Agresta SV. "Current issues in adolescent and young adult cancer survivorship". *Cancer Control Journal* 15.1 (2008): 55-62.

26. Ng AK and Travis LB. "Subsequent malignant neoplasms in cancer survivors". *Cancer Journal* 14.6 (2008): 429-434.

27. Armstrong GT., *et al*. "Long-term effects of radiation exposure among adult survivors of childhood cancer: results from the childhood cancer survivor study". *Radiation Research* 174.6 (2010): 840-850.

28. Levine J., *et al*. "Fertility preservation in adolescents and young adults with cancer". *Journal of Clinical Oncology* 28.32 (2010): 4831-4841.

29. Oeffinger KC., *et al*. "Health care of young adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study". Ann Fam Med 2.1 (2004): 61-70.

30. Hijiya N., *et al*. "Acute leukemia as a secondary malignancy in children and adolescents: current findings and issues". *Cancer Journal* 115.1 (2009): 23-35.

31. Knight KR., *et al*. "Ototoxicity in children receiving platinum chemotherapy: underestimating a commonly occurring toxicity that may influence academic and social development". *Journal of Clinical Oncology* 23.34 (2005): 8588-8596.

32. Skinner R., *et al*. "Risk factors for nephrotoxicity after ifosfamide treatment in children: a UKCCSG Late Effects Group study". United Kingdom Children's Cancer Study Group. *British Journal of Cancer* 82.10 (2000): 1636-1645.

33. Pentheroudakis G and Pavlidis N. "Late toxicities in survivors from adolescent cancers". *Cancer Treatment Reviews* 33.7 (2007): 656-663.

34. Wallace WH. "Oncofertility and preservation of reproductive capacity in children and young adults". *Cancer* 117.10 (2011): 2301-2310.

35. Badawy A., *et al*. "Gonadotropin-releasing hormone agonists for prevention of chemotherapy-induced ovarian damage: prospective randomized study". *Fertility and Sterility* 91.3 (2009): 694-697.

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