Tumors in the Adolescent

Author G. Pentheroudakis

Key words Cancer in the adolescent, juvenile oncology, management, survival.

Summary

Adolescents (15-19 year age group) are affected by malignancies 2-3 times more often than children and adolescent tumors constitute 2% of all malignancies across all age groups. The overall rate of cancer incidence has been rising by 0.9% annually in the 15-19 year age cohort before stabilising in the last decade of the 20th century at an incidence of approximately 200 new cases per million. The most common tumors among adolescents are germ cell malignancies and Hodgkin's disease, followed by central nervous system (CNS) tumors, non-Hodgkin's lymphomas (NHL), thyroid cancer, malignant melanoma, leukemias, soft tissue sarcomas and bone sarcomas. Pediatric embryonal tumors are seldomly encountered, while epithelial carcinomas that commonly affect older adults (breast cancer, colorectal cancer, cervical cancer, lung cancer), occasionally affect adolescents and constitute a non-negligible 20-30% of juvenile tumors. Less than 10% of adolescent malignancies can be attributed to environmental risk factors or genetic conditions, while scant data hint for the presence of a distinct malignant biology compared with histopathologically similar tumors in other age groups. Management of adolescents with cancer has been undertaken by pediatric, hematologic and adult oncologists in various health care models and according to heterogeneous treatment protocols. Despite an overall cure rate of 75%, improvement of long-term survival rates over time in adolescents has lagged behind the substantial improvement of disease control achieved in children and older adults. Delayed diagnosis, lack of access to healthcare, suboptimal management, aggressive tumor biology and lack of clinical/translational research may be among several factors responsible for this. These deficits are now acknowledged and are being confronted jointly by pediatric, hematologic and adult oncology cooperative groups worldwide.

(BJMO 2009;Vol 3;5:191-200)

Introduction

Over the last three decades, the need for specialised care of children with cancer led to the establishment of pediatric oncology as a well-recognised specialty bearing the story of a spectacular success: cure rates have improved from <30% in the 1950s to >75% in the 1990s.[1] Meanwhile, adolescents with cancer have enjoyed much less of this focus for research and improved care, despite the fact that they are 2 to 3 times more numerous than children with cancer. Adolescents, being in the age range of 15-24 years have a higher cancer incidence (2% of all invasive cancers across all age groups) than children (0.75% of all invasive cancers), however with only modest survival improvement.[2] So far, adolescents have been treated in either pediatric or adult oncology units, but they seem in terms of clinical research, management and support, to belong to «no man's land» in most developed societies. Despite harbouring often curable tumors, the recognition of their unique host/disease characteristics, the need for speedy diagnosis, specialised care and support has only recently become evident. Moreover, the lack of substantial improvement of long-term survival of adolescents with malignancies after 1975 was only recently fully acknowledged. As the number of life years lost in this group of young patients is 3-4 times the number of years at age of diagnosis, the need for a progress in disease control at least comparable to that achieved for children or elderly adults is imperative.

Epidemiology

There is no universally accepted common age defi-

nition for adolescence. Functionally, adolescence is defined as the time of onset of puberty, a physiologic threshold that has been decreasing over the past several decades. In several health care systems children are considered those younger than 15 years of age. The World Health Organisation (WHO), though, classifies a child as an individual below 18 years. When both physiological and psycho/socio/economic aspects are taken into account , the end of adolescence equates to 19 years of age in women and 21-25 years of age in men.[3] Using a conventional age range of 15–19 for adolescents, there is ample evidence for an overall higher cancer incidence than that reported in paediatric populations. Data from the *National Cancer Institute's (NCI) Surveillance, Epidemiology and End Results (SEER)* program and the UK cancer registry indicate that the incidence of cancer in adolescents 15–19 years old is 50% higher that in younger persons, with an incidence of 203 new cases per million persons.[4-6] According to SEER and UK registry data, the overall rate of cancer incidence in adolescents has been rising at an average of 0.9% per year. Melanomas, non-Hodgkin lymphomas, soft-tissue sarcomas (mainly Kaposi`s sarcoma) and germ cell tumors have shown the greatest annual increases. However, after 1990 the overall incidence of invasive cancer has not substantially changed in young age groups, indicating that an incidence plateau may have been reached.[7]
The most common tumors among 15–19-year-old adolescents are germ cell malignancies and Hodgkin's disease, followed by central nervous system (CNS) tumors, non-Hodgkin's lymphomas (NHL), thyroid cancer, malignant melanoma, leukemias, soft tissue and bone sarcomas (*Figure 1*). These tumors account for more than 90% of all malignant cases.[8-10] Young patients with NHL usually have diffuse large B-cell or T-cell high-grade histology according to the World Health Organization (WHO) classification, in sharp contrast to the predominance of lymphoblastic and Burkitt types during early childhood. Pediatric embryonal tumors such as nephroblastoma, neuroblastoma, medulloblastoma, hepatoblastoma and retinoblastoma are seldomly encountered, while rhabdomyosarcoma accounts for only a quarter of all soft tissue sarcomas. Epithelial cancers that commonly affect older adults (breast cancer, colorectal cancer, cervical cancer, lung cancer) occasionally do affect adolescents and constitute a non-negligible 20-30% of juvenile tumors. Ethnic/racial differences in incidence are apparent between Caucasian and black youths, with

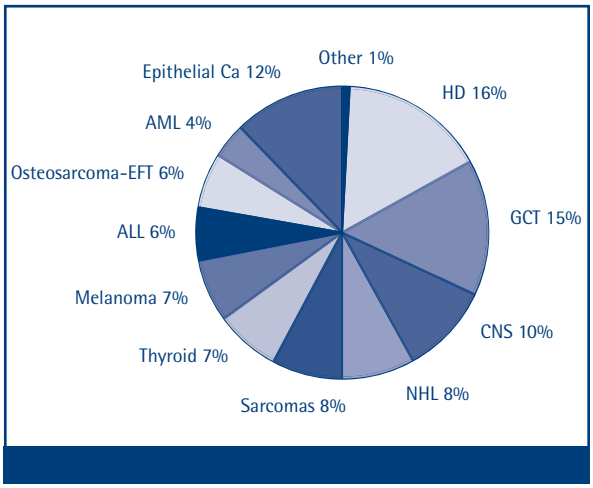

Figure 1. Most common tumors affecting adolescents

cancer appearing 50% more often in whites. The overall frequency of adolescent tumors seems to be equal for both genders or slightly higher for females, in contrast to the male predominance seen in patients older than 50. Acute lymphoblastic leukemia, NHL, Ewing sarcomas, osteosarcomas and brain tumors are more common in males while thyroid carcinomas, melanomas and Hodgkin's disease are diagnosed more often in females.

Etiology

The majority of cancers of adolescence and adulthood are sporadic events of unknown etiology. Genetic conditions account for only a small proportion of malignant cases in these age groups and make up <10% of observed adolescent and young adult tumors. The rare breast/ovarian carcinomas encountered in young females aged <30 may be related to the presence of BRCA1/BRCA2 tumor suppressor gene mutations. However, in one study of women diagnosed with breast cancer before the age of 30, BRCA1, BRCA2, p53 mutations were found in less than 10% of the cases.[11] Similarly, among 77 patients aged 7-19 years, none had a preceding diagnosis of polyposis syndrome and only 10% had multiple colonic polyps.[12] Accordingly, the association of juvenile colorectal cancer with familial adenomatous polyposis or Lynch syndromes (hMLH1/hMSH2,6 mutations) seems to be infrequent.
Similar to genetic factors, environmental factors have rarely been incriminated in the pathogenesis of malignancies of adolescent.[13-15] Exceptions are clear-cell adenocarcinomas of the vagina–cervix in adolescent females, caused by prenatal exposure to

Table 1. Hybrid classification scheme for adolescent and young adult malignancies (Pollock et al [18])

Tumor group	Definition
Group 1	Leukemias
Group 2	Lymphomas
Group 3	CNS tumors
Group 4	Bone tumors
Group 5	Soft tissue sarcomas
Group 6	Germ cell tumors
Group 7	Melanoma and skin carcinoma
Group 8	Carcinomas (except of skin)
Group 9	Miscellaneous specified neoplasms (including embryonal paediatric tumors)
Group 10	Unspecified malignant neoplasms

diethylstilbestrol, hepatic tumors caused by previous hepatitis B/C infection, oral contraceptive use or aflatoxin exposure; melanoma associated with intense exposure to ultraviolet radiation, Kaposi sarcoma, non-Hodgkin`s lymphomas, Hodgkin`s lymphomas and nasopharyngeal carcinoma arising respectively from chronic infection by human herpes virus-8, human immunodeficiency virus and Epstein-Barr virus. Moreover, early-onset chronic infection from high risk HPV strains leads to an increased risk for cervical cancer development at a young age. Adolescents and young adults exposed to radiation or chemoradiation during early childhood occasionally experience second tumors. Most known carcinogens (tobacco, sunlight, diet and chemicals) cause DNA damage in somatic cells resulting in cancer after a delay of more than two decades. Indeed, a reduced incidence of such tobacco-, alcohol-, diet- or sunlight-induced common carcinomas in the adolescent population is the case. However, adolescents should be aware of environmental carcinogens, since exposure to those is often established during this age period and may affect development of cancer at older ages.

Classification

Classification of pediatric tumors is based on morphology (histology), whereas adult tumors are classified according to organ site of the primary (*International Classification of Disease, ICD-O*).[16,17] The epidemiology of malignancy in adolescents represents a transitional phase between that of paediatric embryonal tumors and carcinomas/sarcomas of older adults. Accurate records of population-based patient and host characteristics are necessary in order to develop services tailored to the needs of adolescents with cancer. A diagnostic classification scheme for adolescent cancer is needed so as to meet epidemiological and service planning purposes, study disease characteristics, biology and outcomes as well as assist international cancer registration. Although investigators advocated use of the paediatric classification system, a number of major childhood malignancies are irrelevant in adolescents. Moreover, carcinomas, which occasionally affect youngsters, are inappropriately subdivided in the childhood cancer classification. On the other hand, the adult ICD classification cannot differentiate carcinomas, soft tissue sarcomas and germ cell tumors that arise in many anatomical sites and does not define the important differences between morphological subtypes of carcinomas, CNS and bone tumors. Consequently, neither histology nor organ of origin provides an accurate basis on which to classify the cancers of adolescents. In an effort to produce a separate 'adolescent' nosologic system, *Birch et al* created a morphology-based classification scheme with revised tumor groups specifically for the 15–24 age group malignant epidemiology, using 10 major diagnostic groups defined by ICD-O codes (*Table 1*).[18] These major diagnostic groups are further divided into subgroups based on frequency of occurrence. This hybrid system better accounts for pediatric-like and adult-like malignancies affecting adolescents, better serving as a standard to facilitate comparisons of adolescent cancer incidence across registries or to formulate etiologic hypotheses.

Tumor and host biology

It is currently unclear whether tumors affecting ad-

olescents have a similar or distinct biology from histopathologically identical malignancies harboured by children or older adults.[19] Some evidence suggests that malignant biology may be characterised by molecular aberrations unique for this age-group, however this is sparse and fragmented. Investigators reported that young women had breast carcinomas with frequent deregulation of the phosphatidylinositol 3-kinase (PI3K), MYC and b-catenin pathways, which retained an adverse prognostic significance.[11] Adolescents harbour non-inherited forms of colorectal carcinoma that have no APC, K-RAS mutations, neither loss of heterozygosity at chromosomes 17p, 18q, in contrast to tumors affecting older adults.[20,21] Compared with children, adolescents with acute lympoblastic leukemia (ALL) are more likely to have L2 blast morphology, pro-T cell immunophenotype and the t(9,22) translocation or methylation of the cell cycle control proteins p57, p73.[22] Similarly, young patients with Ewing sarcoma carry 1q gain or 16q losses in their tumors that make them resistant to ifosfamide/etoposide chemotherapy.[23] Patients diagnosed with gastrointestinal stromal tumors before the age of 40 commonly do not harbour KIT or PDGFRb gene mutations in the neoplastic cells.[24] Finally, patients under the age of 50 are diagnosed with thinner, slowly proliferating melanomas harbouring BRAF mutations at a rate 2.5 times higher than in melanomas affecting older individuals.[25]

Adolescents may also have physiological (hormonal), pharmacologic (drug metabolism) and genomic polymorphic characteristics distinct from those of younger or older patients.[22] Hormonal changes during this period or physiological changes affecting volume of distribution, protein binding, hepatic and renal function or drug interactions could alter treatment efficacy and side-effects. Adolescents have an increased incidence of obesity compared to children, a finding associated with poorer outcome in acute leukemias. Moreover, they experience severe neuropathy, diabetes, pancreatitis and osteonecrosis more often than pediatric patients. Gender-related differences in incidence and outcome of melanoma, lymphomas and sarcomas may be due to differences in drug homeostasis. In general, adolescents have healthier renal, liver and bone marrow reserves and are able to tolerate more dose-intensive therapies with chemotherapy and radiotherapy than older patients. Moreover, biopharmacological tolerance and drug metabolism/excretion is superior to what is observed in older adults.

Management and prognosis

The majority of juvenile tumors are potentially curable. Five-year survival rates for ALL, Hodgkin's disease, NHL, sarcomas, germ cell and CNS tumors range from 45% to 90%. Treatment given to a youngster with malignancy often aims for long-term disease control and prolonged survival. Both pediatric oncologists and medical oncologists treating adults may be unfamiliar with management of some of the diverse range of tumors affecting adolescents. The curative aim in the treatment of adolescents necessitates that it is given in a 'state of the art' fashion, as intensive as it needs to be, while avoiding overtreatment and severe late side-effects. Management often consists of combined-modality therapy, incorporating multi-agent chemotherapy, high-dose radiotherapy and aggressive surgery. Cure or failure may depend on factors like adequate dosing, avoidance of unnecessary treatment delays or dose reductions, while skilled and close supportive care are essential to minimise disease- and treatment related symptoms and late consequences. There is evidence from retrospective and cohort studies that the outcome of such patients is superior when treatment is given in a reference cancer centre or in the context of a high-quality clinical trial, attributes reflecting the degree of skill and expertise available in the managing team.[26-29]

Generally, surgery is more readily performed in adolescents who have completed most of their body growth and have fewer comorbidities. Compared with children, they are also less vulnerable to most adverse effects of ionising radiation given to the central nervous, cardiovascular and connective tissue and to the musculoskeletal system, with the exception of sites still developing such as breast and gonads. Chemotherapy can be administered at higher dose-intensities with fewer acute side-effects, though anticipatory vomiting may be enhanced.[7,19]

Despite these advantages, psychosocial issues are more problematic in this patient population. Adolescents may have no parental guidance, a feeling of invincibility, no health insurance, fear for gonadal damage, dependence on self-image and peer-group approval, commitments to school, work or family. All these issues may compromise early diagnosis, access to care and compliance to therapy. Their need for psychological and social support is significant, issues that medical or pediatric oncologists often are poorly equipped to deal with.[30-32]

Adolescents and young adults do not seem to 'fit' in either pediatric wards or medical wards with eld-

Table 2. Survival rates of children and adolescents with cancer.

ICCC group and Subgroup[a]	Europe[b]		United States[c]	
	0-14 years	15-19 years	0-14 years	15-19 years
I. Leukemia	73	44	74	48
Ia. Acute lymphoblastic leukemia	79	50	82	55
Ib. Acute non-lymphoblastic leukemia	49	35	41	41
Ic. Chronic myeloid leukemia	45	37	-	-
II. Lymphomas	84	81	83	86
IIa. Hodgkin's disease	93	89	94	92
IIb,c,e. Non-Hodgkin lymphomas	77	66	77	71
III. Central nervous system tumors	64	70	66	76
IIIa. Ependymoma	58	-	58	91
IIIb. Astrocytoma	75	65	78	76
IIIc. Primitive neurorectodermal tumors	49	-	57	76
IIId. Other gliomas	57	75	53	75
IV. Sympathic nervous system tumors	59	-	66	44
VI. Renal tumors	84	-	90	76
VII. Hepatic tumors	57	-	56	16
VIII. Malignant bone tumors	61	48	68	62
VIIIa. Osteosarcoma	59	52	67	62
VIIIc. Ewing's sarcoma	62	31	65	55
IX. Soft-tissue sarcomas	65	67	73	66
IXa. Rhabdomyosarcoma	63	-	68	46
IXb. Fibrosarcoma	82	81	-	-
X. Germ-cell, trophoblastic and gonodal tumors	84	87	87	91
Xa. Intra-cranial and spinal germ-cell tumors	-	-	74	86
Xc. Gonodal germ-cell tumors	-	90	98	94
XI. Carcinomas and other epithelial tumors	89	88	89	90
XIa. Thyroid carcinoma	98	99	97	99
XIb. Malignant melanoma	86	88	88	93
All cancer	72	73	75	78

[a] *International classification of childhood cancer (ICCC 2nd version*[41]
[b] *Data from*[3,10,18]
[c] *Data from*[19]

erly patients.[33-35] Dedicated units for patients of the 15–19, 15-24 or 15-30 age group staffed by medical oncologistis, pediatric oncologists and hematologists, offer an ideal environment for treatment, interaction with physician, family and peers, skilled nursing care, individualised psychosocial support and coordinated clinical research. Nowadays, most countries recommend referral of adolescents with cancer to specialised centres (model of centralised care) for more effective multidisciplinary treatment.

The *National Institute for Health and Clinical Excellence* in the UK and the *National Cancer Institute* in the US commissioned working groups who produced recommendations for the organisation of optimal care and clinical research of adolescents with cancer.[36,37] Worldwide, suggested models favoured treatment of such patients in pediatric oncology units or medical oncology units for adults according to the tumor diagnosis or treatment in dedicated «juvenile» oncology units with multidisciplinary

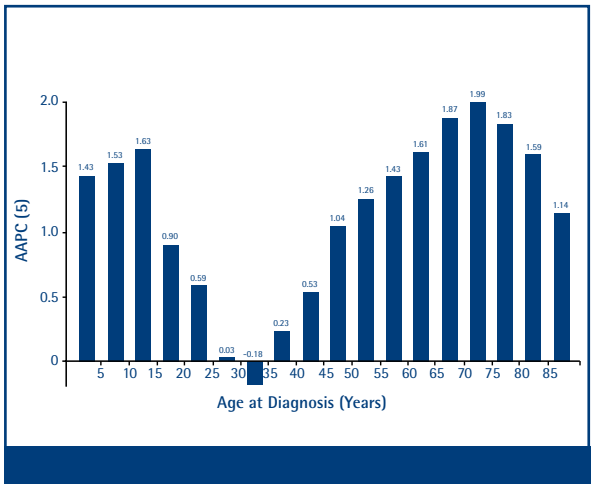

Figure 2. Average annual percent change (AAPC) in 5-year relative survival for all invasive cancers by patient age group, SEER 1975–1997

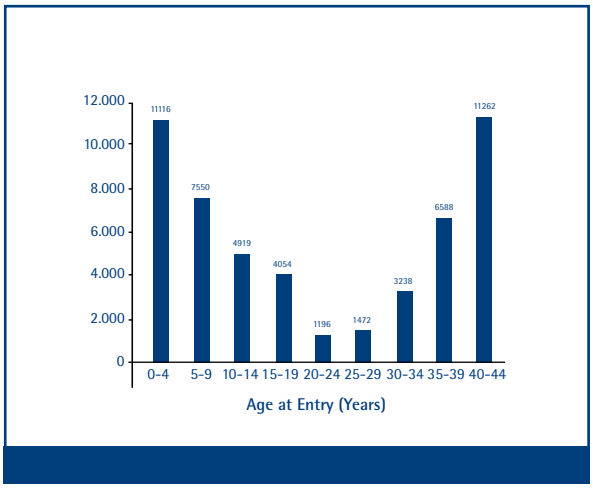

Figure 3. Participation of cancer patients in US National Cooperative Group clinical trials by age group.

staffing. Any adopted model of care should take into account local providers, resources available in the community, cultural, social and financial characteristics and other factors influencing access to care for these patients. Transition of care and identification of the long-term follow-up provider are also critical issues: lifelong follow-up in the treating specialised unit, the use of joint clinics staffed by adolescent oncology specialists and medical oncologists, implementation of a 'transition programme' to transfer the patient's care to either the medical oncologist or the general practitioner have been provided in various parts of the world. At present no gold standard can be identified, as each model has to take into consideration the resources available.[38,39]

Cancer is the second leading cause of non-accidental death in adolescents in Western Europe and the United States (suicide being the first one). In developed societies, the cure rate of adolescents with cancer is 70-75% (*Table 2*).[40] Hematological malignancies, have survival rates ranging from high (92% for Hodgkin`s disease) to intermediate (60-71% for non-Hodgkin`s lymphomas) or relatively low (35-55% for leukemias). For solid tumors, 5-year survival rates of higher than 85% were observed for thyroid cancer, gonadal germ cell tumors and melanomas. Long-term survival rates were intermediate (50-65%) for soft-tissue and bone sarcomas, as well as central nervous system tumors. Adolescents with rare epithelial tumors (breast, cervical, ovarian, colorectal cancers) have a poor survival rate (30-50%) when compared to older adults, an adverse prognosis that can not fully be attributed to delayed diagnosis or presentation at an advanced disease stage. In fact, the survival of adolescents is inferior to that of children for several malignancies, including lymphomas, leukemia, bone and soft-tissue sarcomas, hepatic and CNS tumors.[7,22] The cause of this inferior survival is multifactorial, and most likely the result of a more aggressive tumor biology, delay in diagnosis, poor compliance to therapy and suboptimal management.[19] The only tumors for which an equivalent or superior survival is obtained in adolescents compared to younger or older patients, are testicular, thyroid cancer and melanoma.

The improvement in outcome of youngsters with cancer over the last 30 years is inferior to what has been achieved in pediatric oncologic patients. The relative improvement in 5-year survival rates from 1974 to 1995 has been in excess of 30% for children and only 19% for adolescents aged 15–19 (*Figure 2*). In the recently published *EUROCARE-3 study*, the annual improvement rate of survival in patients aged 15–24 was shown to be inferior to those observed both in children and in adults over the age of 40.[4,19] In 1974, 5-year adolescent survival rates were superior when compared to pediatric patients (64% versus 55%). In sharp contrast, respective figures for the year 2000 are 80% for adolescents versus 85% for children, a reversal in the survival order from a 10% advantage to a 5% deficit.

Clinical research

The success of pediatric oncology is mainly due

to timely diagnosis, optimisation of combined-modality treatment and supportive care. Most of these achievements have been the result of large-scale enrolment and treatment of children with cancer in multicentric clinical trials via an extensive sociomedical infrastructure based on cooperative groups. More than 90% of children with cancer in Europe and the US are treated at institutions that are participating in clinical trials, while only 10% of adolescents do so (*Figure 3*).[41] A perception of poor adolescent compliance to complex protocols, lack of information about trial participation possibilities, lack of health insurance or access to trials, socio-economic factors and exclusion criteria commonly seen in pediatric or adult trials are some of these causes. The lack of clinical research will ultimately hinder the development of more effective or less toxic treatment strategies. Working groups in the US and Europe have begun addressing this problem by setting priorities: analysis of adolescent cancer data retrospectively in published trials and databases, organisation of clinical trials for tumors affecting adolescents jointly by pediatric and adult oncology cooperative groups, banking of biological tissue for translational research and study of host/tumor biology. There is some early evidence of progress over the last decade, as accrual to US NCI trials presented a 42% increase in the 15-19-year old age group in 2003-2005 compared to 2000-2002.[7]

Late effects

Surgery, chemotherapy and radiotherapy have all been incriminated for severe late effects, which are extremely important in the 15–30 age group, where most patients have an excellent outcome and delayed normal tissue injury has ample opportunity to manifest itself after several decades.[42] Aggressive surgery is frequently a cause of late effects interfering with a patient's quality of life, such as retroperitoneal lymphadenectomy causing ejaculatory dysfunction, mutilating surgery in the limbs, head and neck or torso causing disfigurement with resultant functional disabilities.[43] Loss of fertility is a dreaded consequence of chemotherapy, the frequency and duration depending on the dose and type of drugs administered, age and disease. Infertility rates range from 20% to 90% for men and 15% to 75% for females and may also be caused by testicular, ovarian and hypothalamic–pituitary irradiation.[44-47] Germ cell banking and discussion of fertility issues with these patients are as important as those of antineoplastic treatment in relation to the patient's quality of life. Doxorubicin-induced cardiac injury is more common with cumulative administered doses in excess of 550mg/m^2 or combination with mediastinal radiotherapy.[48] Less common toxic effects include pulmonary fibrosis, cerebral atrophy, demyelinisation, leuco-encephalopathy and neurocognitive defects, peripheral neuropathy, ototoxicity, Raynaud's phenomenon, intestinal fibrosis/obstruction, hepatotoxicity, xerostomia/dental problems, and femoral head necrosis.[49,50] Undoubtedly the most dreaded complication of antineoplastic treatment is the occurrence of a second tumor. There is irrefutable evidence from case–control and prospective studies that antineoplastic treatment increases the relative risk of secondary malignancies. Adult survivors of Hodgkin's disease treated with MOPP-like regimens with or without radiotherapy have a relative risk of 16–66% for leukemia, 3–35% for non-Hodgkin's lymphoma and 3–13% for solid tumors. An overall cumulative risk of 20% for any second cancer has been reported at 25 years post-treatment.[51,52] Causal links have been established for radiation therapy with sarcomas, thyroid cancer, breast cancer, lung cancer and leukemias. Cytotoxic agents commonly incriminated for carcinogenesis are alkylators and nitrosoureas. Minimising late toxicity and carcinogenicity while maximising efficacy is one of the toughest challenges that juvenile oncology has to meet today.

Conclusions

The incidence of cancer in adolescents is 2 to 3 times higher than in children, the tumors affecting the former being diverse in histopathology. Cancer kills more youngsters than any other disease, yet it has been under-recognised in this population. Moreover, these tumors are seldomly linked to known environmental, diet, lifestyle or genetic risk factors and may well harbour a biology distinct from that in other age groups. Although the number of life years to be gained is high, adolescents with cancer are not optimally managed, have survival rates inferior to those of children and insufficiently participate in clinical or translational research programmes. These deficits have only recently been appreciated, leading to joint efforts from pediatric oncologists and those treating adults towards early diagnosis, access to optimal care and development of active research infrastructure for our young patients with cancer.

Key messages for clinical practice

1. Cancer occurs in 1 in every 200 adolescents and young adults. There are very few known causes of cancer during adolescence and early adulthood.

2. Adolescents often deny symptoms, are too embarrassed to report them, or attribute them to psychosomatic manifestations.

3. Cancer-related check up should include examination for cancers of the thyroid, testicles, ovaries, lymph nodes, oral cavity, skin, as well as health counseling about tobacco, sun exposure, diet and nutrition, high-risk sexual practices, environmental and occupational exposures.

4. Women should be counseled to undergo cervical smear cancer screening within 3 years after beginning to have vaginal intercourse; they should also be informed about HPV immunisation.

5. Tumors commonly affecting adolescents are germ cell malignancies, leukemias-lymphomas, CNS tumors, thyroid cancer, malignant melanoma, soft tissue and bone sarcomas and rarely epithelial carcinomas. In view of the rarity, curability and the Damocles`sword of late toxic effects, management of these patients should take place in reference centers of excellence.

6. The management of these patients in pediatric oncology, adolescent oncology or medical oncology centers is still a matter of debate and depends on scientific, socioeconomic, cultural and historical factors. Multidisciplinary management is of pivotal significance.

7. Enrollment in clinical trials should be encouraged and psychosocial support should be implemented early on.

8. Expert counseling on fertility issues should take place before initiation of therapy.

9. Long-term follow up is needed for early diagnosis of relapses, late effects of therapy, second tumors and counseling on healthy lifestyle.

References

1. Coleman MP, Babb P Damiecki P et al. Cancer survival trends in England and Wales 1971–1995: deprivation and NHS region. London: HMSO 1999.

2. Bleyer WA. Cancer in older adolescents and young adults: epidemiology, diagnosis, treatment, survival and importance of clinical trials. Med Pediatr Oncol 2002;38:1–10.

3. Alston RD, Rowan S, Birch, et al. Cancer incidence patterns by region and socioeconomic deprivation in teenagers and young adults in England. Br J Cancer 2007;96:1760-66.

4. Ries LAG, Eisner MP, Kosary CL et al. SEER cancer statistics review, 1973–1998. Bethesda, MD: National Cancer Institute 2001. http://seer.cancer.gov/Publications/CSR1973_1998/505.

5. Parkin DM, Kramarova E, Draper GJ et al. International Incidence of Childhood Cancer. Vol II, IARC Scientific Publication no 144. Lyon, France: International Agency for Research on Cancer 1998.

6. Birch JM, Alston RD, Kelsey AM et al. Classification and incidence of cancer in adolescents and young adults in England 1979–1997. Br J Cancer 2002;87:1267–1274.

7. Bleyer A. Young Adult Oncology: the patients and their survival challenges. CA Cancer J Clinicians 2007;57:242-55.

8. Whyte F, Smith L. A literature review of adolescence and cancer. Eur J Cancer 1997;6:137–146.

9. Wu XC, Chen VW, Steele B et al. Cancer incidence in adolescents and young adults in the United States. J Adolesc Health 2003;6:405–15.

10. Stiller C. Epidemiology of cancer in adolescents. Med Pediatr Oncol 2002;3:149–55.

11. Anderson WF, Brinton LA, Chen B, Devesa SS. Qualitative age interactions (or effect modification) suggest divergent pathways for early-onset and late-onset breast cancers. J Clin Oncol 2007;25:21036a.

12. Hill AD. Colorectal carcinoma in childhood and adolescence:

A clinicopathological review. J Clin Oncol 2007;25:5808-14.
13. Melnick S, Cole P, Anderson D et al. Rates and risks of diethylstilbestrol- related clear cell adenocarcinoma of the vagina and cervix: An update. N Engl J Med 1987;316:514–9.
14. Cuzick J, Szarewski A, Cubie G et al. Management of women who test positive for high risk types of human papillomavirus: the HARTstudy. Lancet 2003;362:1871–6.
15. Valagussa P, Bonadonna G. Carcinogenic effects of cancer treatment. In Peckham M, Pinedo H, Veronesi U (eds): Oxford Textbook of Oncology. Oxford: Oxford University Press 1995;2348–58.
16. Kramarova E, Stiller CA. The International Classification of Childhood cancer. Int J Cancer 1996;68:759–65.
17. Percy C, Van Holten V, Muir C. In Muir C (ed.): International Classification of Diseases for Oncology (ICD-O), 2nd edition. Geneva: World Health Organization 1990.
18. Pollock BH, Birch JM. Registration and classification of adolescent and young adult cancer cases. Pediatr Blood Cancer 2008;50:1090-93.
19. Pentheroudakis G, Pavlidis N. Juvenile cancer: improving care for adolescents and young adults within the frame of medical oncology. Ann Oncol 2005;16:181-88.
20. Rajagopalan H, Nowak MA, Vogelstein B, Lengauer C. The significance of unstable chromosomes in colorectal cancer. Nat Rev Cancer 2003;695-701.
21. Chiang JM. Favourable influence of age on tumor characteristics of sporadic colorectal adenocarcinoma: patients 30 years of age or younger may be a distinct patient group. Dis Colon Rectum 2003;46;904-10.
22. Bleyer A, Barr R, Hayes-Lattin B, Thomas D, Ellis C, Anderson B. The distinctive biology of cancer in adolescents and young adults. Nat Rev Cancer 2008;8:288-98.
23. Hattinger CM, et al. Prognostic impact of chromosomal aberrations in Ewing tumors. Br J Cancer 2002;86:1763-69.
24. Prakah S et al. Gastrointestinal stromal tumors in children and young adults: a clinicopathologic, molecular and genomic study of 15 cases and review of the literature. J Pediatr Hematol Oncol 2005;27:179-87.
25. Lu K, et al. Distinct clinical and pathological features are associated with the BRAF-T1799A(V600E) mutation in primary melanoma. J Invest Dermatol 2007;27:900-5.
26. Selby P, Gillis C, Haward R. Benefits from specialised cancer care. Lancet 1996; 348: 313–8.
27. Rauck AM, Fremgen AM, Hutchison CL et al. Adolescent cancers in the United States: A national cancer database (NCDB) report. J Pediatr Hematol Oncol 1999;21:310.
28. Nachman J, Sather HN, Buckley JD et al. Young adults 16–21 years of age at diagnosis entered onto Children's Cancer Group acute lymphoblastic leukemia and acute myeloblastic leukemia protocols. Results of treatment. Cancer 1993;71(10 Suppl):3377–85.
29. Collette L, Sylvester RJ, Stenning SP et al. Impact of the treating institution on survival of patients with poor prognosis metastatic non seminomatous germ cell tumors. J Natl Cancer Inst 1999;91:839–46.
30. Trask PC, Paterson AG, Trask CL et al. Parent and adolescent adjustment to pediatric cancer: Associations with coping, social support, and family function. J Pediatr Oncol Nurs 2003;1:36–47.
31. Larcombe I, Mott M, Hunt L. Lifestyle behaviours of young adult survivors of childhood cancer. Br J Cancer 2002;87:1204–9.
32. Ettinger RS, Heiney SP. Cancer in adolescents and young adults. Psychosocial concerns, coping strategies, and interventions. Cancer 1993;71(10 Suppl):3276–3280.
33. Hollis R, Morgan S. The adolescent with cancer—at the edge of no man's land. Lancet Oncol 2001;2:43–8.
34. Whiteson M. The Teenage Cancer Trust—advocating a model for teenage cancer services. Eur J Cancer 2003;39:2688–94.
35. Leonard R, Coleman R, Gregor A et al. Special problems of adolescents with cancer. J Cancer Care 1995;5:117–20.
36. NICE. Improving outcomes for children and young people with cancer. The evidence review, 2005. http://www.nice.org.uk/pdf/c&typevidencereview.pdf
37. Closing the gap: Research and care imperatives for adolescents and young adults with cancer Report of the Adolescent and Young Adult Oncology Progress Review Group. US Department of Health and Human Services, 2006.
38. Schidlow D, Fiel S. Life beyond pediatrics. Transition of chronically ill adolescents from pediatric to adult health care systems. Med Clin North Am 1990;74:1113–20.
39.B arr R. On cancer control and the adolescent. Med Pediatr Oncol 1999;32:404–10.
40. Desandes E. Survival from adolescent cancer. Cancer Treat Rev 2007;33:609-15.
41. Ferrari A, Montello M, Budd T, Bleyer A. The challenges of clinical trials for adolescents and young adults with cancer. Pediatr Blood Cancer 2008;50:1101-4.Pentheroudakis G, Pavlidis N. Late toxicity in survivors from adolescent cancer. Cancer Treat Rev 2007;33:656-63.
42. Pentheroudakis G, Pavlidis N. Late toxicity in survivors form adolescent cancer. Cancer treat rev 2007;33:656-63.
43. Donohue JP, Foster RS. Retroperitoneal lymphadenectomy in staging and treatment. The development of nerve-sparing techniques. Urol Clin North Am 1998;25:461.
44. Kreuser ED, Hetzel WD, Billia DO et al. Gonadal toxicity following cancer therapy in adults: significance, diagnosis, prevention and treatment.Cancer Treat Rev 1990;17:169–75.
45. Viviani S, Sandoro A, Ragni G et al. Gonadal toxicity after combination chemotherapy for Hodgkin's disease. Comparative results of MOPP versus ABVD. Eur J Cancer 1985;21:601.
46. Constine LS, Woolf PD, Cann D et al. Hypothalamic-pituitary dysfunction after radiation for brain tumors. N Engl J Med 1993;328:87.

47. Radford J, Shalet S, Lieberman B. Fertility after treatment for cancer. Questions remain over ways of preserving ovarian and testicular tissue. BMJ 1999;319:935.
48. Shan K, Lincoff AM, Young JB. Anthracycline-induced cardiotoxicity. Ann Intern Med 1996;125:47–58.
49. Kriesman H, Wolkove N. Pulmonary toxicity of antineoplastic therapy. Semin Oncol 1992;19:508–20.
50. Anderson V, Godber T, Smibert E et al. Neurobehavioural sequelae following cranial irradiation and chemotherapy in children: an analysis of risk factors. Pediatr Rehabil 1997;1:63–76.
51. Van Leeuwen FE, Klokman WJ, Veer MB et al. Long term risk of second malignancy in survivors of Hodgkin's disease treated during adolescence or young adulthood. J Clin Oncol 2000;18:487.
52. Valagussa P. Complications of therapy: Long term side effects. In Cavalli F, Hansen HH, Kaye SB (eds): Textbook of Medical Oncology, 2nd edition. London: M. Dunitz 2000;583–596

Correspondence address

Author: G. Pentheroudakis
Department of Medical Oncology, Ioannina University Hospital, Greece

Please send all correspondence to:
Dr. G. Pentheroudakis
Department of Medical Oncology
Ioannina University Hospital
Niarxou Avenue
45500 Ioannina
Greece.
Tel: 0030 2651099394
gpenther@otenet.gr

Conflicts of interest: the author has nothing to disclose and indicates no potential conflicts of interest.