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Evolving Services for Adolescents with Cancer in Italy: Access to Pediatric Oncology Centers and Dedicated Projects

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Purpose: To describe how the provision of services for adolescents with cancer has evolved in Italy, the study evaluated access to pediatric oncology centers affiliated to the national cooperative group Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP), and the development of dedicated local projects.

Methods: We calculated the observed/expected (O/E) ratio of adolescent patients (15–19 years old) admitted to AIEOP centers during the years 2013–2017. Observed cases were obtained from the AIEOP database (model 1.01). Expected cases were calculated on the incidence rates derived from the population-based registries. In addition, a questionnaire investigated the presence of any formal upper age limits for admitting patients, and to the development of local projects.

Results: In the years 2013–2017, 9534 cases of cancer were registered in the AIEOP database, that is, 8031 children (0–14 years) and 1503 adolescents (15–19 years). The overall O/E ratio was 0.81, that is, 1.06 for children, and 0.37 for adolescents, and differed according the different tumor types. Concerning the questionnaire, 26% of centers reported age limits <18 years. Nineteen centers reported to have local projects dedicated to adolescents.

Conclusions: The study shows an improvement in the services for adolescents in Italy, with an increase percentage of cases treated at AIEOP centers (from 10% of previous study, to 37%), the decrease of centers with admission age limits <18 years (from 44% 10 years ago, to 26%), and the development of many specific local projects. Effective cooperation with adult oncology societies and government recognition remain goals to be achieved.

Keywords: access to care, adolescents with cancer, age limits, dedicated project, expected cases, national program

Introduction

Adolescents with cancer form a subgroup of patients whose clinical management and access to the best possible treatment remain a challenge, especially when compared with improvements related to the children's care model achieved over the years.[1,2] Most importantly, there have been various reports of adolescents having worse survival rates

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than children for many neoplasms, including leukemias and lymphomas, astrocytomas, and bone and soft tissue sarcomas.[3,4] This survival gap cannot be explained by any single factor: it may partly reflect age-related differences in tumor biology and intrinsic aggressiveness, but variables relating to patients' clinical management may have a role as well.[5–9]

Specific programs dedicated to adolescents (and young adults) have been developed in many countries (involving health care providers and various other stakeholders, such as charities, academia, and governments).[2,10,11]

In Italy, a nationwide project began in 2008, promoted by the pediatric cooperative group Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP), aimed to improve adolescents' access to AIEOP centers, the general awareness that adolescents can suffer from cancer, and cooperation with adult medical oncologists. The AIEOP Committee on Adolescents launched various initiatives dedicated to adolescents, with some success stories and some hurdles that still need to be overcome.[12]

A first study conducted by the Committee showed that only 10% of 15- to 19-year-old cancer patients had been treated at AIEOP centers (in the years 1989–2006), compared with 77% of younger patients.[13,14]

The adoption of upper age limits for admission to AIEOP pediatric oncology units was seen as one of the reasons why the AIEOP network was far less effective in serving adolescents than children. In fact, nearly half of the centers had age limits for admission set at 16, 15, or even 14 years.[15] When the first nationwide initiatives for adolescents were getting underway, only two Italian cancer centers had attempted to introduce projects specifically tailored to adolescent patients, that is, the Youth Area Project at the Centro di Riferimento Oncologico in Aviano (developed within an adult medical oncology setting),[16] and the Youth Project at the Istituto Nazionale Tumori in Milan (established at the pediatric oncology unit).[17,18]

This study describes how the provision of services for adolescents with cancer has evolved in Italy. We report on the number of adolescents actually treated at pediatric oncology centers, by comparison with the expected numbers of cases; the adoption of strict upper age limits at pediatric oncology units as a likely barrier to adolescent referrals; and local projects dedicated to adolescents in Italy.

Methods

The study was conducted by the AIEOP Committee on Adolescents. To shed light on the accessibility of AIEOP centers for adolescent patients (15–19 years old) in recent times, we calculated the observed/expected (O/E) ratio of cases admitted to AIEOP centers during the years 2013–2017.

The number of cases observed was obtained from the AIEOP database (Modello 1.01), an *ad hoc* registry that records information on patients treated exclusively at AIEOP centers (50 units in all). It was developed according to the criteria for Advanced Multicenter Research and Security in cooperation with the CINECA (Centro Interuniversitario del Nord Est italiano per il Calcolo Automatico) in Bologna.

The expected number of cases was estimated on the incidence rates derived from the population-based Italian Network of Cancer Registries (Associazione Italiana Registri Tumori [AIRTUM]). The AIRTUM includes 32 general and 5 specialized cancer registries (2 specialized in cancers occurring in childhood and adolescence), and monitors >5.5 million children and adolescents (corresponding to 47% of Italy's population in this age group). The analyses were based on the International Childhood Cancer Classification ICCC-3 and included all malignant tumors.

The expected number of cases in the years 2013–2017 was still unavailable, so we used the figures already published for 2011–2015, based on AIRTUM's observed incidence rates in 2003–2008.[19] Although we used incidence figures of 10 years older than those of observed cases, we believe that this did not influence the analysis because no major epidemiologic or demographic changes were documented over the two periods in Italy. A trend for an increasing incidence of tumors in children and adolescents was registered in Italy until 1997, but not later (i.e., in the 1998–2008 period).[20] Based on these data, we assumed that the incidence remained stable over the study period.

The O/E cases of cancer in adolescents were compared with the ratio for children (0–14 years old). The adopted methodology was the same as used in previous AIEOP studies on O/E ratio.[13,14]

We also analyzed the proportions of children and adolescents admitted to the various AIEOP centers.

A questionnaire prepared by the AIEOP Committee on Adolescents was sent in electronic form to all AIEOP centers to obtain details of any formal upper age limits for admitting patients. The questionnaire also investigated whether centers had any local projects dedicated to adolescents (and if not, why), and what such projects involved (e.g., dedicated staff, spaces, and facilities). Finally, respondents were asked to indicate any further aspects to prioritize in the next years to better manage adolescent cancer patients.

Results

Observed and expected cases

In the years 2013–2017, there were 9534 cases of cancer registered in the Modello 1.01 database by 50 AIEOP centers: 8031 were children (0–14 years old) (84%), and 1503 were adolescents (15–19 years old) (16%). As regards population-based registries data, we would have expected 11,647 cases, including 7580 patients 0–14 years of age (65%) and 4067 at 15–19 years (35%).

The overall O/E ratio was 0.81, that is, 1.06 for children and 0.37 for adolescents. Table 1 provides the observed and expected cases, and the O/E ratios by tumor diagnosis and patient's age.

Considering the adolescent cohort and the group of tumors most common in this age group, the O/E ratio was 1.01 for bone sarcomas, 0.66 for leukemias, 0.55 for soft tissue sarcomas, 0.51 for central nervous system tumors, 0.33 for lymphomas, 0.32 for germ cell tumors, and 0.07 for epithelial tumors and melanoma.

The proportion of adolescent cases expected in the whole cohort of patients 0–19 years of age was 35%. For the AIEOP network as a whole, the proportion of observed cases was 16%. This proportion varied at different centers, and exceeded 20% only for 6 of the 50 AIEOP centers.

Questionnaire: upper age limits for patient admissions

The questionnaire was answered by 38 of the 50 AIEOP centers (76%). Among the 38 centers participating in the

Table 1. Number of Children (0–14 Years Old) and Adolescents (15–19 Years Old) with Cancer Diagnosed and Registered in the AIEOP Mod.1.01 Database in 2013–2017 (O) Versus Number of Cases Expected (E) in Italy in 2011–2015, Based on AIRTUM Incidence Rates Observed in 2003–2008

ICCC-3	*Age*	*0–14 years*				*15–19 years*			
		O	*E*	*O/E*	*(95% CI)*	*O*	*E*	*O/E*	*95% CI*
I	Leukemia	2699	2253	1.20	1.15–1.24	283	430	0.66	0.58–0.73
II	Lymphoma and reticuloendothelial neoplasm	874	1105	0.79	0.74–0.84	430	1311	0.33	0.30–0.36
III	Central nervous system tumors	1572	1549	1.01	0.96–1.10	212	418	0.51	0.44–0.57
IV	Sympathetic nervous system tumors	665	547	1.22	1.12–1.30	18	10	1.80	0.97–2.63
V	Retinoblastoma	130	157	0.83	0.69–0.97	0	0	—	—
VI	Renal tumors	333	350	0.95	0.85–1.05	11	19	0.58	0.24–0.92
VII	Hepatic tumors	70	81	0.86	0.66–1.07	5	17	0.29	0.04–0.55
VIII	Malignant bone tumors	404	363	1.11	1–1.22	180	179	1.01	0.86–1.15
IX	Soft-tissue and other extraosseous sarcomas	561	453	1.24	1.14–1.34	135	244	0.55	0.46–0.65
X	Germ cell, trophoblastic and other gonadal neoplasms	403	216	1.87	1.68–2.05	123	384	0.32	0.26–0.38
XI	Other malignant epithelial neoplasms and melanoma	176	352	0.50	0.43–0.57	66	973	0.07	0.05–0.08
XII	Other and unspecified malignant neoplasms	144	154	0.94	0.78–1.09	40	82	0.49	0.34–0.64
	Total	8031	7580	1.06	1.04–1.08	1503	4067	0.37	0.35–0.39

AIEOP, Associazione Italiana Ematologia Oncologia Pediatrica; AIRTUM, Associazione Italiana Registri Tumori; CI, confidence interval; E, expected; O, observed.

survey, 10 (26%) reported that patient admissions were subject to age limits <18 years (i.e., at 14, 15, or 16 years old), but these cutoffs were not always binding, and older patients might often be admitted and treated. The age limit was reportedly 18 years at 20 centers (53%), whereas it was 21–24 years at 4 (10.5%), and the last 4 centers (10.5%) reported having no upper age limit for patient admissions.

Questionnaire: local projects dedicated to adolescents

According to the results of our survey, 19 centers have local projects dedicated to adolescents. Table 2 outlines the peculiarities of each project, as reported by the centers. The other 19 centers have no such dedicated projects, the reasons reportedly being a lack of resources and staff at 9 centers, and the small number of adolescent patients admitted at 4, whereas this question was not answered by the other 6 centers.

Table 3 provides the key issues to prioritize in the management of adolescent cancer patients, according to the answers given in the questionnaire.

Discussion

This study sheds light on how the provision of services for adolescents with cancer has evolved in the Italian pediatric oncology network. It shows that the percentage of adolescents treated at AIEOP centers has increased over the years, with the O/E ratio rising from 10% in 1989–2006[13] to 28% in 2007–2012,[14] to 37% in 2013–2017.

The O/E ratio differs in the different tumor types, for example, from 1.01 for bone sarcomas to 0.07 for epithelial tumors and melanoma. These differences reflect different service organization (e.g., the well-structured cooperation between pediatric and adult medical oncology societies for the management of bone sarcomas) and imply different recommendations. In fact, it is clear that the significance of the gap between observed and expected cases among adolescents is quite different for pediatric-type malignancies and adult-type cancers.

Survival advantages have been reported for adolescent patients with many pediatric-type tumors in those cases where they are treated at pediatric instead of adult medical oncology services.[21–24] For these tumors, it is mandatory that pediatric oncology centers can implement initiatives to increase the referral of adolescent patients. On the contrary, adult oncologists have more experience in treating patients with melanoma and carcinomas. Although it might be that could be reasonable that a large proportion of adolescents with these tumors was referred to adult centers, adolescents need also age-specific environment and services that are usually found in pediatric oncology ward and not in adult medical oncology ward. The real challenge, therefore, may be the multidisciplinary management of adolescent patients involving both pediatric and adult oncologists and the development of dedicated centers with age-specific facilities.

The O/E analysis has some limits, that is, observed cases were those admitted at AIEOP centers during the 2013–2017 period, whereas expected cases were estimated from incidence rates in 2003–2008 (however, there were no major epidemiologic or demographic changes over the two periods in Italy)[20]; center-by-center O/E ratio was not available (we cannot calculate expected numbers); epidemiology on rare diseases (and therefore small numbers) has limitations (this factor, in addition to the increasing number of foreigner patients referred to AIEOP centers, can explain the O/E ratio above 1—that means more cases observed than expected—observed in some cancer types, especially in children) (Table 1).

As further finding, our study shows that nowadays only a minority of AIEOP centers still set age limits for patient admission <18 years: they are pediatric oncology units with low patient volumes, and their age limits are reportedly not binding. This should be seen as an important improvement *vis-à-vis* the situation described 10 years ago, when 44% of AIEOP centers imposed age limits at 16, 15, or even 14 years.[15] Therefore, upper age limits, previously considered a major barrier to a better adolescent cancer patient management, should be currently considered a minor issue.

Our survey also showed that 19 AIEOP centers (Table 2) now have specific projects in place for adolescents (10 years

Table 2. Local Projects Dedicated to Adolescents at AIEOP Centers

Center	*Description*
Centro di Riferimento Oncologico, Aviano	''Youth Area''; multidisciplinary staff including doctors, nurses, youth workers, psychologists, fertility experts; dedicated spaces; numerous activities (e.g., diary-writing and other artistic and creative projects; projects with schools in local area; projects with pairs)
Pediatric Oncology Unit, Istituto Nazionale Tumori, Milan	''Youth Project''; dual goal concerning medical issues (e.g., access to treatment protocols, preserving schemes) and support measures (dedicated spaces, creative and artistic activities to give young patients new ways to express themselves—music, fashion, creative writing, photography, theatricals); dedicated staff with doctors, nurses, youth workers, psychologists, artistic coordinators; supported by the local parents association
Pediatric Hematology/Oncology, Ospedale Pediatrico Bambino Gesù, Roma	''4You'' project; multidisciplinary staff including doctors, nurses, youth workers, psychologists, volunteers, cancer survivors; supportive projects in the ward; programs outside the hospital (project with local schools)
Pediatric Department, San Gerardo Hospital, Fondazione MBBM, Monza, Italy	Limited dedicated staff (doctor, psychologist); dedicated spaces; specific project: ''WAI radio''; supported by the local parents association
Pediatric Onco-Hematology, Regina Margherita Children's Hospital, Torino	Staff with age-specific skills; dedicated spaces; various programs: a specific project dedicated to job orientation; project on transition to adult care; project with radio (''radio UGI''); supported by the local parents association and charity
Pediatric Department, Policlinico Bari	''We Young''; dedicated staff (psychologists, volunteers, music therapist); specific projects: cosmetic make-up, song writing, murals, sport, pet therapy supported by the local parents association and charity
Pediatric Oncology Unit, Policlinico San Matteo, Pavia	Effective multidisciplinary cooperation with adult medical oncology/hematology unit; dedicated spaces (''Easy Room''); no dedicated staff supported by the local parents association and charity
Pediatric Oncology Unit, Meyer Hospital, Firenze	Dedicated staff, coordinated by psychologists; laboratories for artistic projects supported by the local parents association and charity
Pediatric Oncology Unit, Parma University Hospital	Managed by psychologists; dedicated spaces; laboratories: radio-web, cosmetic make-up, photography
Pediatric Oncology Unit, Pisa University Hospital	''Young Group,'' managed by the local parents association; social activities; sport supported by the local parents association
Pediatric Oncology Unit, Catanzaro Hospital	Managed by psychologists and volunteers; laboratories for artistic projects
Pediatric Oncology Unit, ''Vito Fazzi'' Hospital, Lecce	Dedicated spaces; specific program for off-therapy patients
Pediatric Oncology Unit, Policlinico Gemelli, Roma	Dedicated spaces; creative projects: music, cooking, painting, theater
Pediatric Oncology Unit, ''Casa Sollievo Della Sofferenza,'' San Giovanni Rotondo	Developed by the local parents association; dedicated spaces; project with local schools
Pediatric Oncology Unit, ''Burlo Garofolo'' Hospital, Trieste	Age-specific psychosocial support; staff: psychologists, physiotherapists
Pediatric Oncology Unit, ''S.M. Della Misericordia'' Hospital, Perugia	Age-specific psychosocial support; social and recreational programs
Pediatric Department, Filippo Del Ponte Hospital, Varese	Age-specific psychosocial support; art therapy project supported by the local parents association and charity
Department of Women's and Children's Health, Padova University Hospital	Dedicated spaces (''Teen Zone''); dedicated staff supported by the local parents association and charity
Pediatric Oncology Department, Policlinico Sant'Orsola Malpighi, Bologna	Dedicated staff; dedicated spaces; developed by the local parents association

ago, only two Italian centers had attempted to organize tailored projects for them). All the largest centers have developed dedicated projects. Of note, the Youth Area in Aviano is developed within an adult medical oncology setting, whereas all other projects are implemented in the pediatric oncology wards. A general feature of the AIEOP centers' local projects is to run creative and artistic laboratories designed to give young patients novel ways to express themselves.[25–28] As other common features, AIEOP projects are reported to be generally coordinated by psychologists and supported by the local parents associations or charities.

If our study demonstrates that the landscape for adolescents with cancer in Italy has changed for the better in the last decade, much remains to be done. The O/E ratio is still not satisfactory, considering the now commonly recognized benefits of treating adolescents with cancer at pediatric

Table 3. Key Issues to Prioritize for Adolescent Cancer Patient Management, According to the Respondents Answering Our Questionnaire

More resources
Dedicated spaces and staff
Formal recognition of programs as standard of care
More national cooperation
International cooperation
Better cooperation with adult oncologists
Access to new drugs
Age-specific clinical trials
Recognition of the specificity of ''adolescent oncology''
Development of networks among young patients

oncology units, for both clinical (in particular for pediatric-type neoplasms)[21–24] and psychosocial reasons. In addition, although the ultimate goal of eradicating the disease is often accomplished, surviving adolescent cancer is not without cost, for example, post-therapy infertility, loss of school years, loss of friends, and so on. These problems can only be prevented with specific programs tailored on adolescents with cancer.

Table 3 lists some of the issues considered crucially important by the AIEOP centers answering our questionnaire. Among others, they indicated the need for more resources and for the formal recognition of youth projects as part of standard care. They also identified a greater degree of national and international cooperation,[29] and more collaboration with the world of adult oncology as important goals to pursue.

The improvement in the services for adolescents in Italy may be at least partly because of the successful communication strategy of the AIEOP Committee on Adolescents, involving various initiatives to improve the scientific community's awareness, and educational projects designed for teenagers and their families. In particular, it is worth mentioning the campaign, ''There's no reason why'' (to improve awareness that cancers can occur in adolescence too),[30] the campaign *#fattivedere* (an Italian term with the dual meaning of ''Don't hide!'' and ''Get a check-up'') to help young people to interpret any symptoms they experience, seek medical advice, and arrive at an earlier diagnosis),[31] and the ''Winners' Cup'' (a football tournament for adolescents with cancer, or a history of cancer; in its third edition in 2019, young people from eight different European countries were involved).[32]

Although some such initiatives proved successful, others were less so. A national project called SIAMO (Società Italiana Adolescenti con Malattie Onco-ematologiche [Italian Society for Adolescents with Oncohematological Diseases]) was launched in 2014,[33,34] as an extension of the AIEOP Committee on Adolescents. Its aim was to create a broad-based, comprehensive national platform together with adult oncology scientific societies (and other stakeholders, such as parents associations). Unfortunately, efforts to develop a genuinely effective collaboration between pediatric and adult oncologists failed, probably because the project was mostly expression and feeling of pediatric community. Given the lack of support from the National Health Service and government, the SIAMO project was abandoned in June 2018.

The AIEOP Committee on Adolescents is continuing its activities—in fact, providing services for adolescents with cancer seems to be a matter for pediatric oncologists, in Italy at least. Although our study shows that some progress has been made, the experiences of other countries that have embarked on national programs[2,35–40] point to the strong need for pediatric and adult oncologists to work together. Institutional recognition is also important for projects to be sustainable. Local programs should be part of a comprehensive national approach, and should become a standard of care: for this to happen, the vision and practical schemes adopted by local and national programs need to be sustained by the regional and national government and the National Health System, thus achieving a virtuous interaction that can really brighten the horizon for adolescents with cancer in our country.

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