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Short Communication

Adolescents with cancer in Italy: Entry into the national cooperative paediatric oncology group AIEOP trials

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ABSTRACT

Purpose: Survival of adolescents (15–19 years old) with cancer has shown less favourable improvement in comparison with survival rates for younger children and older adults. This might be partly explained by the relative lack of participation of adolescents in cooperative clinical protocols.

Methods: This analysis compares the number of 15- to 19-year-olds treated at the paediatric oncology centres affiliated to the AIEOP (and registered in the 'model 1.01') with the number of incident cases predicted in Italy based on incidence rates from the Italian network of cancer registries (AIRTum).

Results: By 2006, over 22,000 cases had been registered in the model 1.01, and 1743 of these were adolescents. The ratio of observed/expected (O/E) cases of 15- to 19-year-olds was 0.10 (as opposed to 0.77 for the 0–14-year-old children), and this ratio increased from 0.05 to 0.18 over three successive study periods (1989–1994, 1995–2000 and 2001–2006). Sarcomas were the neoplasms with the highest O/E ratios, with 0.28 and 0.43 for osteosarcoma and Ewing sarcoma and 0.33 and 0.39 for rhabdomyosarcoma and other soft-tissue sarcomas, respectively. In the period 1989–2006, 55% of the adolescents registered (versus 69% of the children) were enrolled in formal national trials.

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Conclusion: Our study confirms a lower referral of 15- to 19-year-old adolescents to paediatric oncology units and their under-representation in clinical trials, but we also observed a progressive improvement in this situation in recent years.

1. Introduction

Approximately 800 adolescents, aged 15–19 years old, are diagnosed with cancer each year in Italy.[1] Neoplasms are the second major cause of death in adolescents after accident injuries.[2] In recent years, various reports have suggested that survival trends in adolescents and young adults with cancer have been disappointing compared with the improvements in survival achieved in younger children and older adults.[3] It has also been claimed that this lack of progress in the adolescents' survival trend may have something to do, at least in part, with their relative lack of participation in cooperative clinical trials.[3–6] This situation is plainly in contrast with that of younger children, whose more effective treatment and considerably improved survival rates reflect not only refinements in diagnostic tools and therapeutic strategies, but also the benefits derived from the inclusion of patients in cooperative clinical trials.[7]

Since the 1970s, Italian paediatric oncologists have been developing cooperative protocols through the Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP), which has played a major role in designing and implementing nationwide clinical trials. In 1989, the AIEOP Operational Office in Bologna established a hospital-based registry (the 'model 1.01') for collecting demographic details and essential clinical data on children and adolescent patients with tumours diagnosed at AIEOP centres.[8] The database has registered about 75% of all childhood cancer cases in Italy (80% in the Northern and Central regions, 65% in Southern Italy), based on the predicted number of cases in Italy.[1] The main aims of the registry were to create a national (albeit not exhaustive) record of paediatric cancer cases, to assess internal migrations and access to childhood cancer care centres, as well as to monitor the accrual of patients in clinical trials.

Thus, the model 1.01 can be used to analyse the number of adolescents with cancer referred to the centres of the AIEOP network and enrolled in clinical trials, and to compare those numbers for children. This paper reports on the adolescent cases listed in the AIEOP model 1.01 database in three successive 6-year periods from 1989 to 2006. Information on type of cancer and age at diagnosis for each case was available in the AIEOP database, allowing comparison of the number of cases recorded in the database with the incidence rates obtained from the Italian population-based registries (AIRTum network). Reporting on the results of specific clinical trials goes beyond the scope of the present paper.

2. Patients and methods

This analysis compared the numbers of adolescents with cancer (aged 15–19 years old)[9] treated at 55 paediatric oncology centres affiliated to the AIEOP network with the expected numbers of patients calculated from the incidence rates derived from the population-based AIRTum network.

The AIEOP model 1.01 database is kept according to the criteria for Advanced Multicentre Research and Security in cooperation with the CINECA (Centro Interuniversitario del Nord Est italiano per il Calcolo Automatico), Bologna. As of 2006, 55 clinical facilities treating children and adolescents with cancer were operating nationwide. The cases observed were classified by year of diagnosis in three periods (1989–1994, 1995–2000 and 2001–2006).

The model 1.01 records information on patients treated only in AIEOP centres. All the paediatric oncology units in Italy are affiliated to AIEOP. The database includes patients enrolled in AIEOP clinical trials and patients not enrolled in such protocols who were treated according to protocols/schemes in use at a specific institution or those given tailored treatments, as well as patients taking part in international clinical studies differing from the AIEOP trials. In Italy, with a few exceptions for older patients with peculiar paediatric disease (i.e. neuroblastoma, rhabdomyosarcoma, medulloblastoma), it is standard practice to admit patients up to 18 years of age into paediatric units. The eligibility criteria for the large majority of AIEOP clinical trials include 0–18 year old patients. Patients treated outside an AIEOP centre can not usually be enrolled in AIEOP trials.

The prediction of the number of adolescent cancer cases in Italy was based on the age-specific incidence rates recorded by the Italian network of cancer registries (AIRTum) in 1998–2002.[1] The AIRTum database pools data drawn from 22 general registries and three specialist registries (two on childhood and adolescent cancer, one on female breast cancer) and covers 32.9% of the Italian resident population in the 0- to 14-year-old age bracket (approximately 2,660,000 children per year), and 26.9% of the 15- to 19-year-old subjects (800,000 adolescents). The database is updated regularly and submitted to quality control procedures developed according to the most recent international parameters and specific software developed by the AIRTum. All diagnoses are coded using the ICD-O-2 classification.[10] The expected numbers were calculated for major and minor categories in the International Childhood Cancer Classification.[11] The same analyses were conducted for children 0–14 years old with cancer registered in the AIEOP model 1.01 database between 1989 and 2006. The childhood and adolescent population in Italy decreased in size over the study period, from approximately 9,100,000 and 4,000,000 in 1989–1994 to approximately 8,200,000 and 2,900,000 in 2001–2006, respectively.

The statistical significance of the differences between the observed (O) and expected (E) numbers of cases was tested by calculating confidence intervals (CI) around the O/E ratio according to the Fieller method proposed by Silcocks.[12] Statistical significance was defined as the 95% confidence interval

Table 1 – Number of adolescents with cancer (15–19 years old) diagnosed between 1989 and 2006 and registered in the AIEOP Model 1.01 database (O) versus the expected (E) number of cases in Italy based on the AIRTum incidence rates.

Period of diagnosis	1989–2006				1989–1994	1995–2000	2001–2006	P*
	O	E	O/E	(95% CI)	O/E	O/E	O/E	
Leukaemia	344	1682	0.20	(0.18–0.23)	0.08	0.21	0.37	<0.001
Acute lymphocytic leukaemia	215	940	0.23	(0.20–0.26)	0.07	0.24	0.43	<0.001
Acute non-lymphocytic leukaemia	107	501	0.21	(0.17–0.26)	0.09	0.22	0.38	<0.001
Lymphoma and reticuloendothelial neoplasms	520	5533	0.09	(0.09–0.10)	0.04	0.09	0.17	<0.001
Hodgkin lymphoma	361	4043	0.09	(0.08–0.10)	0.03	0.08	0.18	<0.001
Non-Hodgkin lymphoma	152	1125	0.14	(0.11–0.16)	0.08	0.14	0.21	<0.001
CNS tumours	178	1230	0.14	(0.12–0.17)	0.06	0.16	0.24	<0.001
Ependymoma	17	49	0.35	(0.17–0.58)	0.21	0.50	0.36	0.546
Astrocytoma	67	470	0.14	(0.11–0.18)	0.04	0.16	0.26	<0.001
Primitive neuroectodermal tumours	64	155	0.41	(0.30–0.55)	0.20	0.44	0.68	<0.001
SNS tumours	22	136	0.16	(0.09–0.24)	0.07	0.18	0.26	<0.001
Neuroblastoma and ganglioneuroblastoma	21	49	0.43	(0.23–0.70)	0.21	0.50	0.64	<0.001
Retinoblastoma	2	–	–	–	–	–	–	–
Renal tumours	10	68	0.15	(0.05–0.26)	0.15	0.18	0.11	0.489
Hepatic tumours	11	49	0.22	(0.09–0.40)	0.00	0.38	0.36	0.119
Malignant bone tumours	275	989	0.28	(0.24–0.32)	0.20	0.29	0.36	<0.001
Osteosarcoma	114	402	0.28	(0.23–0.35)	0.15	0.32	0.44	<0.001
Ewing sarcoma	158	365	0.43	(0.36–0.52)	0.39	0.42	0.50	<0.001
Soft-tissue sarcomas	217	866	0.25	(0.21–0.29)	0.12	0.23	0.46	<0.001
Rhabdomyosarcoma and embryonal sarcoma	93	278	0.33	(0.26–0.42)	0.22	0.27	0.57	0.015
Fibrosarcoma, neurofibrosarcoma and other fibromatous neoplasms	10	297	0.03	(0.01–0.06)	0.01	0.04	0.06	<0.001
Other specified soft-tissue sarcomas	74	192	0.39	(0.29–0.50)	0.16	0.35	0.74	<0.001
Germ cell, trophoblastic and other gonadal neoplasms	75	1997	0.04	(0.03–0.05)	0.01	0.04	0.08	<0.001
Gonadal germ cell tumours	27	1546	0.02	(0.01–0.02)	0.00	0.03	0.02	0.387
Carcinomas and other malignant epithelial neoplasms	54	3641	0.01	(0.01–0.02)	0.00	0.01	0.04	<0.001
Thyroid carcinoma	13	1144	0.01	(0.01–0.02)	0.01	0.01	0.02	0.084
Melanoma	6	1057	0.01	(0.00–0.01)	0.00	0.00	0.02	0.083
Other and unspecified malignant tumours	16	501	0.03	(0.02–0.05)	0.02	0.01	0.07	0.216
Total	1745	16,711	0.10	(0.10–0.11)	0.05	0.10	0.18	<0.001

* P-value for trend across periods of diagnosis.

not including the reference value. All analyses were conducted using SAS 8.2 statistical software.

3. Results

By 2006, over 22,000 cases of cancer had been registered in the AIEOP database: 1745 were 15–19 years old (the proportion of patients under 18 remained around 85% throughout the whole period); 312 were diagnosed in 1989–1994, 559 in 1995–2000, and the remaining 874 in 2001–2006. Table 1 shows the numbers of adolescents with any type of tumour registered in the AIEOP database and the predicted numbers of cases in Italy, based on the AIRTum incidence rates (16,711 cases in all, i.e. 6580 in the first period, 5389 in the second and 4742 in the third).

The O/E ratio was calculated for the entire period and also for the three successive periods: the overall O/E ratio was 0.10, and it rose from 0.05 to 0.18 from the first to the third period of observation, respectively. For all tumour types, except for renal, hepatic, gonadal neoplasia, ependymoma thyroid carcinoma and melanoma, a statistical significant trend in the O/E ratio was observed across periods of diagnosis. Sarcomas had the highest O/E ratios, with 0.28 and 0.43 for osteosarcoma and Ewing sarcoma, respectively, and 0.33 and 0.39 for rhabdomyosarcoma and other soft-tissue sarcomas. Between 2001 and 2006, the number of adolescents referred to AIEOP centres with these types of tumour accounted for about half of the expected number of cases.

The O/E ratio was around 0.20 for leukaemias (rising to 0.40 in the last of the three periods), and around 0.10 for lym-

Table 2 – Number of children with cancer (0–14 years old) diagnosed between 1989 and 2006 and registered in the AIEOP Model 1.01 database (O) versus expected (E) number of cases in Italy based on the AIRTum incidence rates.

	O	E	O/E	(95% CI)
Leukaemia	7967	8512	0.94	(0.91–0.97)
Acute lymphocytic leukaemia	6576	6762	0.97	(0.94–1.01)
Acute non-lymphocytic leukaemia	1237	1315	0.94	(0.87–1.02)
Lymphoma and reticuloendothelial neoplasms	2910	4437	0.66	(0.63–0.69)
Hodgkin lymphoma	1214	1927	0.63	(0.59–0.68)
Non-Hodgkin lymphoma	1579	1336	1.18	(1.10–1.27)
CNS tumours	2948	5258	0.56	(0.54–0.59)
Ependymoma	349	542	0.64	(0.56–0.74)
Astrocytoma	1160	1824	0.64	(0.59–0.68)
Primitive neuroectodermal tumours	840	1076	0.78	(0.71–0.85)
SNS tumours	1900	1969	0.96	(0.91–1.03)
Neuroblastoma and ganglioneuroblastoma	1850	1892	0.98	(0.92–1.04)
Retinoblastoma	446	449	0.99	(0.87–1.13)
Renal tumours	1104	1343	0.82	(0.76–0.89)
Wilms tumour, rhabdoid and clear cell sarcoma	1051	1179	0.89	(0.82–0.97)
Hepatic tumours	227	253	0.90	(0.75–1.07)
Hepatoblastoma	176	124	1.42	(1.13–1.80)
Malignant bone tumours	1009	1163	0.87	(0.80–0.94)
Osteosarcoma	468	475	0.99	(0.87–1.12)
Ewing sarcoma	508	441	1.15	(1.01–1.31)
Soft-tissue sarcomas	1408	1357	1.04	(0.96–1.12)
Rhabdomyosarcoma and embryonal sarcoma	735	624	1.18	(1.06–1.31)
Fibrosarcoma, neurofibrosarcoma and other fibromatous neoplasms	133	258	0.52	(0.41–0.63)
Other specified soft-tissue sarcomas	292	284	1.03	(0.87–1.21)
Germ cell, trophoblastic and other gonadal neoplasms	616	770	0.80	(0.72–0.89)
Gonadal germ cell tumours	263	336	0.78	(0.66–0.92)
Carcinomas and other malignant epithelial neoplasms	236	1118	0.21	(0.18–0.24)
Thyroid carcinoma	43	294	0.15	(0.10–0.20)
Melanoma	31	281	0.11	(0.07–0.15)
Other and unspecified malignant tumours	79	755	0.10	(0.08–0.13)
Total	21,053	27,384	0.77	(0.76–0.78)

phomas. For central nervous system (CNS) and sympathetic nervous system (SNS) tumours, the O/E ratio was around 0.15, but it was significantly higher for certain histotypes, such as ependymoma, CNS primitive neuroectodermal tumours and neuroblastoma ($p < 0.001$). For gonadal tumours and carcinomas or other malignant epithelial neoplasms, the O/E ratio was much lower, ranging from 0.01 to 0.04.

During the same overall study period, 21,053 children 0–14 years old with cancer were registered in the AIEOP database (Table 2). The predicted number of cases was 27,384. The O/E ratio was 0.77, and remained steady in the three study period. The O/E ratio was over 0.80 for leukaemias, non-Hodgkin's lymphoma, neuroblastoma, retinoblastoma, nephroblastoma, hepatoblastoma, and bone and soft-tissue sarcomas, while it was 0.56 for CNS tumours and 0.21 for carcinomas or other malignant epithelial neoplasms.

Table 3 shows the proportions of patients included in the AIEOP clinical trials based on expected cases and on cases registered in the AIEOP model 1.01. Overall, the proportion of children and adolescents enrolled in AIEOP clinical trials was 53% and 5.5%, respectively ($p < 0.001$). Among patients 'not enrolled' in AIEOP protocols, the percentages of children and adolescents included in international cooperative protocols not formally defined as AIEOP trials were 9% and 6%, respectively.

4. Discussion

This study analysed the rates of registration of adolescents with cancer at reference paediatric oncology centres affiliated to the Italian AIEOP cooperative group and their enrollment in cooperative national paediatric clinical protocols. Though no data are available on where and how patients not seen at AIEOP centres may have been treated (and, in principle, it is possible that that some of them were enrolled into adult trials), our findings strongly underscore the problem of the limited proportion of adolescents entering cooperative paediatric groups and protocols (although from two-thirds to three-quarters of all cancers occurring in adolescence are tumours commonly seen in paediatric age).[3] Significant data on this issue have already been reported in other Western countries (in the United States, Canada[13–19] and United Kingdom,[20,21] for instance, the rate of enrolment in clinical trials was reportedly around 20% or lower for 15–19 year olds and over 50–60% for children). Being under-represented in clinical trials

Table 3 – Percentages of cases enrolled in AIEOP clinical trials in Italy (A) and patients registered in the AIEOP Model 1.01 database (B), by age group.

Age at diagnosis	A			B		
	0–14	15–19	P*	0–14	15–19	P*
Leukaemia	84.0	15.2	<0.001	89.4	76.2	<0.001
Acute lymphocytic leukaemia	92.2	20.1	<0.001	95.1	87.4	<0.001
Acute non-lymphocytic leukaemia	64.2	14.3	<0.001	68.3	68.2	0.983
Lymphoma and reticuloendothelial neoplasms	48.2	4.9	<0.001	73.0	54.0	<0.001
Hodgkin lymphoma	53.7	5.0	<0.001	85.3	55.7	<0.001
Non-Hodgkin lymphoma	77.2	6.8	<0.001	65.4	48.7	<0.001
CNS tumours	18.7	4.2	<0.001	33.4	30.3	0.394
Ependymoma	34.3	8.2	0.026	53.6	23.5	0.015
Astrocytoma	17.4	4.2	0.005	27.2	29.9	0.630
Primitive neuroectodermal tumours	33.2	16.0	0.005	42.5	39.1	0.596
SNS tumours	69.8	6.5	<0.001	72.7	40.9	0.001
Neuroblastoma and ganglioneuroblastoma	72.3	18.4	<0.001	73.8	42.9	0.001
Retinoblastoma	59.9	–	–	60.5	100.0	0.254
Renal tumours	47.3	3.0	0.005	57.7	20.0	0.016
Hepatic tumours	58.3	14.0	0.004	64.8	63.6	0.935
Malignant bone tumours	43.4	16.9	<0.001	49.9	60.4	0.002
Osteosarcoma	34.6	13.3	<0.001	34.9	47.4	0.013
Ewing sarcoma	76.0	29.9	<0.001	66.1	69.6	0.414
Soft-tissue sarcomas	68.4	15.7	<0.001	65.8	62.7	0.372
Rhabdomyosarcoma and embryonal sarcoma	88.6	23.1	<0.001	75.1	69.9	0.278
Fibrosarcoma, neurofibrosarcoma and other fibromatous neoplasms	26.2	1.2	0.076	50.4	40.0	0.526
Other specified soft-tissue sarcomas	64.2	27.9	<0.001	62.3	71.6	0.136
Germ cell, trophoblastic and other gonadal neoplasms	34.0	1.3	<0.001	42.5	32.0	0.081
Gonadal germ cell tumours	40.0	0.4	<0.001	51.3	18.5	0.001
Carcinomas and other malignant epithelial neoplasms	2.9	0.2	0.242	14.0	16.7	0.611
Thyroid carcinoma	1.4	0.0	0.668	9.3	0.0	0.254
Melanoma	1.1	0.2	0.836	9.7	16.7	0.614
Other and unspecified malignant tumours	1.9	0.4	0.667	19.0	12.5	0.536
Total	53.0	5.5	<0.001	68.8	55.0	<0.001

* P-value for equality of proportions.

has already been identified as a factor likely to lower a patient's chances of cure, thus this under-representation may help to explain the relatively weaker improvement in survival rates observed over the years in adolescents than in children or older adults.[4–6,13–21]

It is worth noting, however, that the proportion of adolescents treated at paediatric oncology facilities in Italy has clearly been improving over the years. The O/E ratios for bone and soft-tissue sarcomas were around or above 0.50 in the last period, while for acute lymphocytic leukaemia it increased to 0.43. The ratio remained low for tumour types more typical of young adult age (i.e. germ-cell tumours and carcinomas), but the fact that most of these cases were referred to adult centres (probably more used to dealing with such neoplasms than paediatric facilities) may be considered acceptable. The O/E ratio stayed low for CNS tumours (for both children and adolescents), with the exception of the subtypes systematically requiring post-operative radiotherapy and chemotherapy (e.g. primitive neuroectodermal tumours), and this is probably influenced by the large proportion of patients with low-grade neoplasms treated by neurosurgeons and never referred to AIEOP oncology centres.

As for the formal inclusion of Italian patients in AIEOP clinical trials, our study showed that, overall, the adolescent enrolment rate was lower than that observed for children, but not dramatically so (55% versus 69%). The proportion of adolescents enrolled was very high for cases of acute lymphocytic leukaemia, and better than that of children for adolescent patients affected by bone sarcomas (probably reflecting the active cooperation between the AIEOP and the Italian Sarcoma Group [ISG], which facilitated the elaboration of shared clinical trials for both children and adults). Data on enrolment in AIEOP clinical trails should be evaluated with some caution, however, because different findings for different tumour types may reflect different strategies being adopted by the various working groups over the years, regarding the development of national protocols but also their participation in international trials not formally defined as AIEOP trials or the activity of referral single institutions with their own protocols.

The increasing referral rates observed for adolescents in Italy in recent years parallels the significant improvement seen in other countries (e.g. in North America, in particular for patients with sarcoma),[5,16] thanks to multiple-level com-

prehensive efforts and the development of committees tailored to adolescents and young adults (AYA).[3,22] However, from currently available data, it is hard to say whether the recently observed increasing entry rates will lead to a better outcome for adolescent patients, although some published studies focusing on different tumour types would suggest a survival advantage for patients enrolled in clinical trials and/or treated according to paediatric protocols instead of adult schemes (or even when they are treated according to the same protocol, but at paediatric instead of adult centres).[23–32]

On the other hand, it is becoming apparent that probably neither the paediatric oncology model of care (mainly family-focused) nor the adult medical oncology model (more disease-focused) are ideally suited to the complex needs of adolescent patients. The best solution might ultimately be that of creating a new model (completely patient-focused) and a new discipline, i.e. 'adolescent and young adult oncology'. However, while awaiting for this, the access of adolescent patients to optimal cancer services may also be improved by increasing the availability of the clinical trials (sometimes they are not actually available due to age limits adopted by hospitals or clinical trial planners, which may exclude otherwise eligible patients), and by improving the cooperation between paediatric and adult oncologists.[4] In fact, despite the potential cultural and logistical difficulties, simply striving to improve the cooperation between paediatric oncologists and adult medical oncologists may prove very important, since this should be a challenge for both sides and sharing their expertise could have synergistic effects (e.g. by pooling the paediatric oncologists' experience of multidisciplinary cooperative protocols with the adult oncologists' experience of novel therapies).

In conclusion, our study provides an overview of the Italian paediatric oncology world and the problem of access to paediatric care for adolescent cancer patients. We documented the poor referral of 15- to 19-year-olds to paediatric oncology units and their under-representation in clinical trials, but also the improvement seen in recent years, now that the international cancer community has recognised that teenagers deserve special attention. We believe that future progress in the treatment of cancer in patients of this age group will depend largely on increasing their participation in clinical trials.

Conflict of interest statement

None declared.

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Appendix

List of the chairpersons of the AIEOP Centres, as of December 2006:

Madon E (Torino), Bona G (Novara), Dini G (Genova), Carnelli V, Fedeli F, Fossati Bellani F, Roncarolo MG (Milano), Masera G (Monza-MI), Locatelli F (Pavia), Cornelli PE (Bergamo), Porta F (Brescia), Nespoli L (Varese), Carli M (Padova), Marradi P (Verona), Grotto P (Belluno), Rossetti F (Monselice), Battisti L (Bolzano), Tamaro P (Trieste), Nocerino A (Udine), Izzi G (Parma), Paolucci P (Modena), Pession A (Bologna), Borgna Pignatti C (Ferrara), Vecchi V (Rimini), Bernini G (Firenze), Morgese G (Siena), Favre C (Pisa), Aversa F (Perugia), Pierani P (Ancona), Felici L, Visani G (Pesaro), Di Marzio A (Pescara), Castello MA, De Rossi G, Donfrancesco A, Foà R, Menichelli A, Riccardi R (Roma), Casale F, Poggi V (Napoli), Amendola G (Nocera Inferiore), Ladogana S (S Giovanni Rotondo-FG), Presta G (Tricase), Pozzi S (Lecce), De Mattia D (Bari), Magro S (Catanzaro), Nobile F (Reggio Calabria), Sperlì D (Cosenza), Aricò M (Palermo), Schilirò G (Catania), Gallisai D (Sassari), Argiolu F (Cagliari).

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