«Juvenile» oncology - a missing subspecialty. The experience of a reference cancer centre

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Introduction. **Despite unique tumor epidemiology and a higher cancer incidence compared to pediatric patients, adolescents and young adults have not been receiving specialized, multidisciplinary, centralized care. In an effort to emphasize this need, we present outcome and toxicity data from a reference centre.**

Methods. **Cohort of 150 patients aged 15-30 treated for malignant tumors of lymphoid and solid organs from 1986 to 2002.**

Results. **Patients aged 15-19 commonly had lymphomas, germ cell tumors and pediatric sarcomas, whereas those aged 20-30 experienced germ cell tumors, lymphomas, melanomas and epithelial tumors more often. Overall 5- and 10-year survival was 80%, whereas 5-year and 10-year time to treatment failure was 68% and 43.5% respectively. 24% of patients experienced persistent, late treatment-related toxicities that interfered with their normal lifestyle.**

Conclusion. **Despite the need for specialized care, psychosocial support and enrollment in clinical trials, youngsters have not been recognized as a patient group with distinct needs. Development of «Juvenile» oncology is required.**

Key words: cancer, chemotherapy, adolescents, young adults, juvenile oncology.

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INTRODUCTION

During the last four decades, the need for intensive, specialized treatment, care and support by skilled personnel along with the curability of childhood cancers led to the establishment of pediatric oncology as a well-recognized subspecialty. This has been the story of a spectacular success: cure rates have improved from less than 30% in the fifties to approximately 75% in the nineties[1], owing to financial investment, multidisciplinary research efforts and the development of a unique cooperative infrastructure throughout the world. Meanwhile, the next oldest age group of cancer patients enjoyed much less of the thrive for research and improved care than their younger counterparts. Despite the observation of both higher and accelerated cancer incidence in the 15-30 year age group in comparison to children along with only modest survival improvement[2], adolescents and young adults remained an «orphan» of the continuously specializing oncological clinical sciences. In this retrospective analysis, we aim to emphasize distinct features of both tumors and patients of the 15-30 year age group as well as the imperative need for specialized management, support and research by presenting summary epidemiological, toxicity and outcome data on 150 young patients with cancer treated at a Greek reference oncology centre.

MATERIAL AND METHODS

This retrospective analysis studied all patients managed for malignant tumors of lymphoid and solid organs (except for leukemias) requiring chemotherapy with an age at diagnosis between 15 and 30. These patients were treated between 1986 and 2002 at the department of medical oncology of the Ioannina University Hospital, a reference centre treating all patients with cancer living in the North-West of Greece.

All patients received suitable antineoplastic treatment as deemed appropriate by the scientific standards prevailing at the time of diagnosis. The patients had histologic, cytologic or serologic diagnosis of malignant disease followed by any combination of surgery, chemotherapy or radiotherapy.

Information on geographical area of residence, personal medical history, family history of malignancy and current health status were obtained on first consultation of the patient and recorded in the case sheets. Clinical records were updated with information on treatment administered, toxicities and clinical

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outcome, familial tumor clustering, environmental exposure, job and lifestyle changes at each patient visit. At the time of the analysis, all data were retrieved from the clinical records and transferred to an electronic database for ease of processing.

Definition of survival functions, late toxicity and statistical methods

Overall survival was calculated from the date of diagnosis to the date of death or last follow-up. Relapse-free and progression-free survival (as well as time to treatment failure) were calculated from the date of diagnosis to the date of disease relapse and disease progression or date last seen, respectively. All patients were followed-up in predefined time intervals according to the diagnosis, stage of malignancy and administered treatment. Late toxicity manifestations were defined as treatment-induced side-effects that persisted for more than 12 months from the completion of antineoplastic treatment, had clinical significance for either patient or physician and severely interfered with the patient's normal lifestyle and work.
Data analysis was performed for all patients for whom clinical records were available. The «retrospective» primary endpoint was overall survival for all patients and by tumor-specific subgroups. Secondary endpoints were relapse-free and progression-free survival both for all patients and by tumor-specific subgroups, as well as late toxicity and familial clustering data. Survival was examined using the Kaplan-Meier product limit method.

RESULTS

Patient and treatment characteristics

From 1986 until 2002, 150 patients (82 male, 68 female) were managed for localized or disseminated cancer of solid or lymphoid organs. Patients with leukemia were managed in the department of hematology and thus, are not included in our registry. A significant percentage of patients with gliomas were managed in the department of neurology, not being included in our registry. All patients were in the 15-30 age group at the time of diagnosis (median 23). The most common tumors were testicular cancer and Hodgkin's disease, followed by non-Hodgkin's lymphomas (NHL), germ cell ovarian cancer and breast cancer. These tumors accounted for more than 2/3 of the total of malignant cases. All 16 patients with NHL had high-grade histology according to the World Health Organization (WHO) classification. Patient characteristics are summarized in table 1.
Among 48 patients in the 15-19 age group, the most common tumors were Hodgkin's disease, testicular cancer, germ cell ovarian tumors and sarcomas. Characteristic in this age group is the rarity of common epithelial tumors and melanomas (fig. 1). In the 102 patients belonging in the 20-30 age group, NHL, breast cancer and melanomas made their appearance along with the «usual suspects», Hodgkin's disease, testicular cancer and ovarian germ cell tumors (fig. 2). All patients received 2 to 18 (median 6) chemotherapy cycles. Six patients received myeloablative chemotherapy with autologous hemopoietic support, usually at the time of relapse of testicular cancer, Hodgkin's disease or non-Hodgkin's lymphomas. 94 young patients had undergone definitive surgical resection of the primary tumor, whereas 46 received radiotherapy at some point in the course of their management.
No strong evidence for genetic background of malignancy was evident from the family history of affected youths as only 6/150 patients had one first-degree relative diagnosed with cancer and none had two or more. In only two cases an identical tumor type was

TABLE 1. **Patient characteristics**

Total number of patients n = 150
Male/female ratio 82/68
Median age at diagnosis (range) 23 (15-30)

Tumor histology	N
Testicular cancer	31
NSGCT	(25)
Seminoma	(6)
Hodgkin's disease	29
Non-classical LP	(2)
Classical	
Nodular sclerosis	(17)
Lymphocyte-rich	(5)
Mixed cellularity	(5)
NHL	16
Ovarian germ cell tumour	13
Breast cancer	13
Ewing family tumour	7
Soft tissue sarcoma	6
Osteosarcoma	5
Colorectal cancer	4
Melanoma	4
Carcinoid	3
Glioma	3
Langerhans cell tumours	2
GTN	2
CUP	2
NPC	2
Ovarian-epithelial cancer	1
Ovarian-granulosa cell	1
Mesothelioma testis	1
Gastric cancer	1
Hepatoma	1
Small intestinal cancer	1
Renal cancer	1
Anal cancer	1

NSGCT: non seminomatous germ cell tumours; NHL: non Hodgkin's lymphomas; LP: lymphocyte predominant; GTN: gestational trophoblastic neoplasia; CUP: cancer of unknown primary; NPC: nasopharyngeal carcinoma.

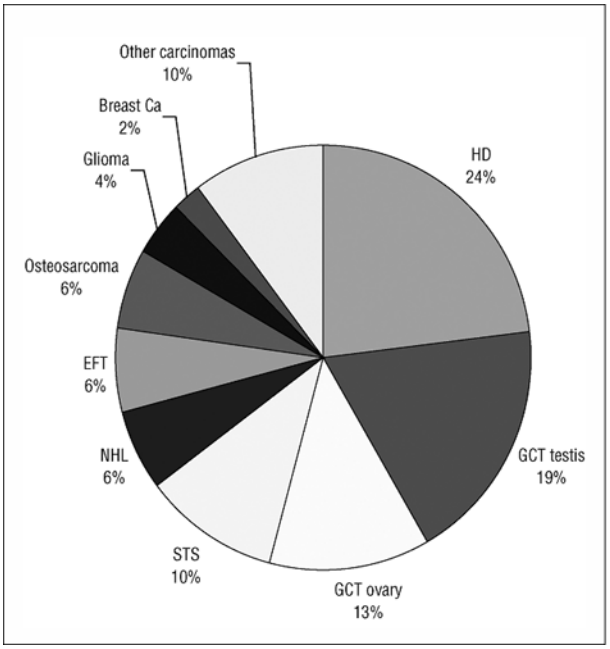

Fig. 1. % Incidence of tumours in age group 15-19 (n = 48). HD: Hodgkin's disease; GCT: germ cell tumour; STS: soft tissue sarcoma; NHL: non-Hodgkin's lymphoma; EFT: Ewing family tumours.

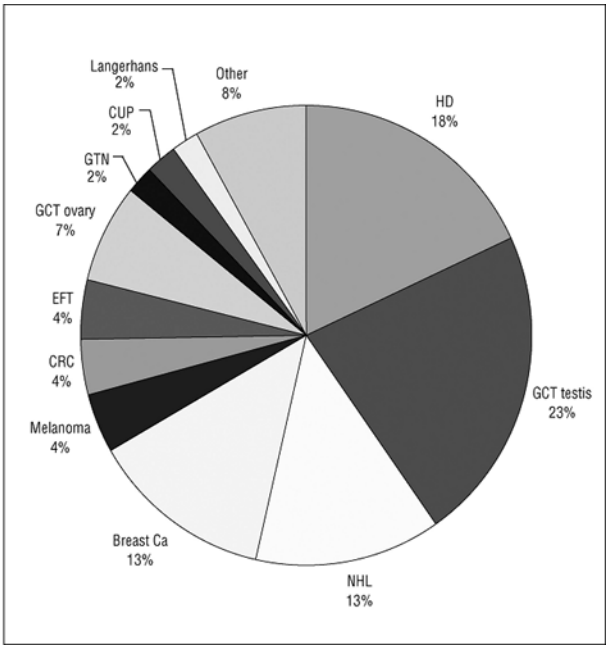

Fig. 2. % Incidence of tumour types in 20-30 age group (n = 102). HD: Hodgkin's disease; GCT: germ cell tumour; NHL: non-Hogkin's lymphoma; EFT: Ewing family tumours; CRC: colorectal cancer; GTN: gestational trophoblastic neoplasia; CUP: carcinoma of unknown primary.

diagnosed in the patient and the first-degree relative (Hodgkin's disease and breast cancer). No evidence of geographical clustering of tumor types emerged from data processing.

Survival data

With a median follow-up of 64 months (range 1-137), 25 relapses of malignant disease and 22 deaths occurred. The cause of death was progression of malignancy in 20 patients, whereas one patient with Burkitt's lymphoma died from neutropenic sepsis during the course of chemotherapeutic management. Another patient was cured from Hodgkin's disease after receiving 6 cycles of ABVD-MOPP chemotherapy and mediastinal irradiation but died from sudden cardiac death nine years later without any evidence of disease relapse. Overall survival for all 150 patients was 80% both at 5-years (95% CI 72-88) and 10-years (95% CI 70-86). Of considerable interest is the occurrence of late relapses 3-10 years post diagnosis, highlighted by the relapse of a patient with Hodgkin's disease more than 12 years after his presentation. For the 132 patients for whom data were available, the median time to treatment failure (TTF) was 118 months (95% CI 104-132), defined by a 5-year disease free survival of 68% (95% CI 58-79) and a 10-year disease-free survival of 43.5% (95% CI 21-66) (fig. 3).

Analysis of overall survival and time to treatment failure data by tumor type was less reliable because of the limited number of patients and was only implemented for the most common tumor types. Data are summarized in table 2. Survival rates were particularly higher for testicular cancer, Hodgkin's disease and germ cell ovarian cancer, in contrast to patients with breast and sarcomatoid solid tumors (table 2).

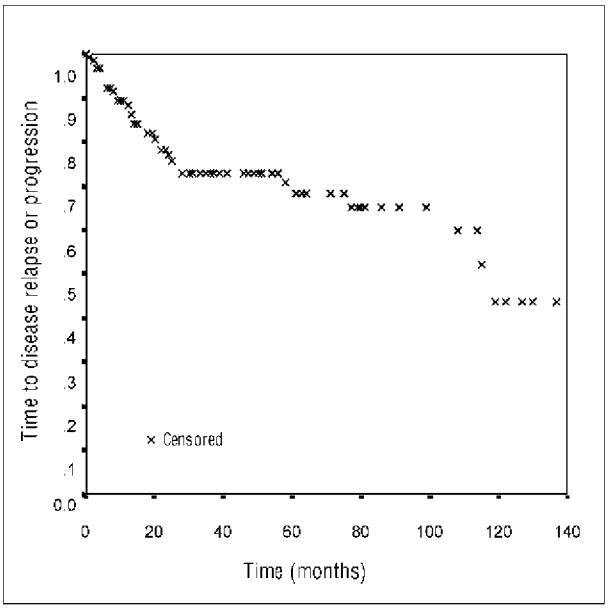

Fig. 3. Time to treatment failure for 132 patients with available data.

TABLE 2. **Survival data by tumor type**

Tumor type	OS	DFS/PFS
Hodgkin's disease	5-year 100%	5-year 96%
N = 29	10-year 100%	10-year 56%
Non-Hodgkin's lymphomas	5-year 69%	5-year 74.5%
N = 16		
Testicular cancer	5-year 85%	5-year 80%
N = 31	10-year 85%	10-year 80%
Germ cell ovarian cancer	5-year 92%	5-year 92%
N = 13	10-year 92%	10-year 92%
Breast cancer	5-year 72%	5-year 40%
N = 13		
Sarcomas	5-year 66%	5-year 20%
N = 18		

OS: overall survival; DFS/PFS: disease or progression-free survival.

Youngsters with sarcomas (n = 18) were a heterogeneous group with diagnoses of Ewing family tumors (7), osteosarcomas (5) and soft tissue sarcomas (6). Thus, the poor survival outcome is not representative of each malignancy and is mainly due to the poor survival of those patients who had advanced soft tissue sarcomas.

Late toxicity data

Late, permanent toxic manifestations were experienced by 24% of the young patients (36/150), as shown in table 3. None of the patients studied developed a second tumor up to the time of the analysis. The most common late effects were persistent neurotoxicity (n = 9), infertility (n = 8), postoperative pain, femoral head necrosis and lymphedema (each n = 3). All the cases of neurotoxicity were graded as II (n = 7) or III (n = 2), a common denominator being persistence and interference of paresthesias with normal life and absence of significant improvement over a period of several years. All of these patients were exposed to high cumulative doses of neurotoxic chemotherapeutic drugs, such as cisplatin, taxanes and vinca alkaloids. The cases of infertility consisted of permanent azoospermia in five males and permanent amenorhoea in three females who received high cumulative doses of alkylating agents, nitrosoureas and/or cisplatin. Persistent postoperative pain was seen in youngsters who had undergone pelvic or thoracic surgery for resection of the primary tumor. The three patients who experienced femoral head necrosis had received cytotoxic combinations with high-dose steroids, the latter being incriminated in the pathogenesis. Other late effects were seen less often, but when present, their impact on the young patients' quality of life was severe. Two patients with Hodgkin's disease who received doxorubicin in total dose of more than 300 mg/m^2 had echocardiographic evidence of absolute left ventricular ejection fraction decline of more than 10%, one of them succumbing to sudden cardiac death nine years later.

TABLE 3. **Incidence of late toxicity**

Persistent or late toxicities 36/150 patients (24%)	
Toxicity	N
Neurotoxicity	9
Infertility	8
Lymphedema	3
Femoral head necrosis	3
Postoperative pain	3
Cardiotoxicity	2
Endocrine dysfunction	2
Post RT neuropathic pain	2
Proctitis	2
Ototoxicity	2
Cognitive deficits	2
Fatigue	2
Malabsorption	1
Bladder constriction	1
Hepatotoxicity	1
Pulmonary fibrosis	1
Raynaud	1
RT pneumonitis	1
Depression	1
Xerostomia	1

DISCUSSION

The incidence of cancer in young patients aged 15 to 30 years is higher and rising faster than in children[3,4]. The most common tumors in the 15-30 age group are Hodgkin's disease, germ cell tumors, CNS tumors, non Hodgkin lymphomas, acute lymphoblastic leukemia and sarcomas[6]. It must be emphasized that this distribution is unique and not encountered in either younger or older age groups. Common childhood cancers such as Wilms tumor, neuroblastoma, medulloblastoma, ependymoma, retinoblastoma and hepatoblastoma are not seen whereas carcinomas of the aerodigestive and genitourinary tracts seen in older patients are rare.

The whole «juvenile» 15-30 age group can be split in two distinct subgroups[5,7]: Adolescents aged 15-19 are commonly diagnosed with «pediatric-type» tumors such as osteosarcoma, rhabdomyosarcoma, Ewing sarcomas, gliomas, leukemias/lymphomas and represent a transitional phase in tumor epidemiology between childhood and older adults. Young adults aged 20-30 seem to experience Ewing sarcomas, osteosarcomas, embryonal sarcomas, acute lymphoblastic leukemia and CNS gliomas less often than their 15-19 year old counterparts. On the other hand, Hodgkin's disease, NHL, germ cell tumors are commoner while melanomas and aerodigestive tumors make their

first, though still rare, appearance. Despite the skewness inherent in our patient population due to non-referral of leukemia and glioma patients and lack of representation of young patients who did not receive chemotherapy (thyroid cancer, early stage germ cell tumors, and some sarcomas), our experience seems to support these data. This highlights the mixed epidemiology of pediatric and adult-type cancers that prompted some investigators to call for the development of a new nosologic system for their classification[8].

Little is known about the cause of the increase in cancer incidence or the cause of cancer in general in the adolescent and young adult patient group. Indeed, very few tumors have been attributed to environmental or inherited factors[9]. Most common carcinogens (diet, smoke, sunlight, chemicals) take more than one or two decades of exposure before induction of malignant transformation although data suggest that intensive ultraviolet light exposure in the second decade of life may lead to development of melanomas after a short latent period[2,8]. Among our four melanoma patients, two developed the primary in sites not exposed to the sun (trunk), further supporting the lack of environmental risk factors. The rarity of common aerodigestive, skin and genitourinary tumors in our registry is in keeping with this short period of exposure to carcinogens.

Most young patients are diagnosed with potentially curable malignancies and receive some form of combined-modality treatment. The survival figures from our patient series depict the curability of the common juvenile tumors. For some tumor types, relapse-free survival data contrast strikingly to the overall survival data, depicting the successful salvage of relapsing patients with modern treatment strategies[5]. Still, improvement in survival in older adolescents has lagged behind the improvement in children. The relative survival improvement that has occurred in the last thirty years was 31-38% for pediatric patients, compared to only 19% for adolescents and young adults[2,3]. To build further on this less optimistic picture, most common «juvenile» tumors are associated with a worse prognosis in adolescents-young adults than in children, with the notable exception of germ cell tumours[2,10-11]. A possible cause for this lack of progress in the 15-30 age-group may be the lack of participation in clinical trials (the only way to conduct clinical research and develop new treatments). Participation in trials has been as low as 2-6%, being named «the adolescent and young adult gap» and waits explanation[12]. Indeed, only eight of our patients did participate in a clinical trial. This was due to unavailability of trials for the 15-18 year age group, reluctance to impose an additional burden to a struggling patient, characterization of the adolescent as non-compliant and belief that most such patients fare well. Another point that has to be taken from this series is the present risk of recurrence of malignancy, even late ones occurring more than 5 years from the date of diagnosis. The rate of late relapse may have been underestimated and emphasizes the need for strict follow-up of «cured» youngsters who adhere poorly to follow-up protocols, being in a competitive and creative phase of their lives[13].

Adolescents and young adults have to be treated by skilled personnel in the presence of an appropriate infrastructure, in view of their need for aggressive treatment, psychosocial and supportive care. These patients face several challenges such as education, sexual maturation, employment, marriage, reproduction, parenting, insurability on top of a struggle for reconciliation with diagnosis, for cure and survival[14,15]. Moreover, late toxicities of aggressive treatment are dreaded and have been well described in the medical litterature[16-18]. They are probably not so important anywhere than in this group, where most patients have an excellent outcome and delayed normal tissue injury has ample opportunity to manifest itself after several decades. Confirmation of this experience is evident in our cohort with the sudden cardiac death of a patient cured from Hodgkin's disease. More patients did experience a severe compromise of their quality of life due to treatment-induced late effects while a risk-taking behavior and «unhealthy» lifestyle often seen augments normal tissue injury[19].

In conclusion, distinct tumor biology and epidemiology, need for aggressive toxic treatment, lack of clinical research, lack of survival improvement comparable to pediatric patients, requirement for intensive psychosocial-supportive care and occurrence of late toxicities have been repeatedly documented in young patients with cancer. These are sufficient reasons for the oncologic community to take up the call and lead the way for the development of Juvenile Oncology, a subspecialty that has to fulfill pressing expectations.

COMPETING INTERESTS

The authors declare no competing interests.

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