Università degli Studi di Padova

Dipartimento di Salute della Donna e del Bambino - SDB

DOTTORATO DI RICERCA IN MEDICINA DELLO SVILUPPO E SCIENZE DELLA PROGRAMMAZIONE

INDIRIZZO DI EMATOONCOLOGIA, IMMUNOLOGIA E GENETICA

Ciclo XXIV

TITOLO

ANALISI DI NUOVE STRATEGIE TERAPEUTICHE PER PAZIENTI IN ETÀ PEDIATRICA AFFETTI DA TUMORI SOLIDI REFRATTARI ALLA CHEMIOTERAPIA STANDARD

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OBIETTIVI E SOMMARIO

L'attività di ricerca del Dottorato si è svolta presso la Clinica di Oncoematologia Pediatrica del Dipartimento di Pediatria dell'Università degli Studi di Padova.

Il programma del dottorato si è sviluppato in un contesto di ricerca clinica ai fini dello studio di "nuove" strategie terapeutiche per i pazienti pediatrici affetti da tumori solidi recidivi/refrattari.

Il Nostro Centro costituisce uno dei maggiori Centri di Emato-Oncologia pediatrica in Italia ed è il Centro Coordinatore per i sarcomi delle parti molli a livello Nazionale.

In Italia esiste, come è noto, una rete di rapporti tra i centri di Emato-Oncologia Pediatrica che permette di seguire i bambini affetti da patologia neoplastica in modo omogeneo e coordinato. La partecipazione attiva ai Protocolli terapeutici dell'Associazione Italiana di Emato-Oncologia Pediatrica (AIEOP) e il contributo costante nell' elaborazione dei Protocolli stessi da parte del Nostro Centro, costituisce uno dei punti fermi dell'attività clinica e scientifica. Per quanto attiene alla patologia in discussione (tumori solidi dell'infanzia), il Nostro Centro ha inoltre funzioni di coordinamento a livello europeo nell'ambito del protocollo per la cura dei sarcomi delle parti molli EpSSG 2005.

Il Nostro Centro nell'attività scientifica e clinica quotidiana collabora, tra gli altri, con:

• AIEOP: Associazione Italiana di Emato-Oncologia Pediatrica
• EpSSG: European Protocol Soft Tissue Sarcoma Group
• EPOC: European Paediatric Oncology Off-patent Medicines Consortium
• INT Mi: Istituto Nazionale Tumori di Milano
• IOV: Istituto Oncologico Veneto
• ITCC: Innovative Therapies for Children with Cancer

Il nostro lavoro si è pertanto concentrato sui pazienti in età pediatrica, adolescenziale e del giovane adulto affetti da tumore solido (in particolare Rabdomiosarcoma recidivo/refrattario).

Una prima parte del lavoro si è focalizzata sullo studio della popolazione di pazienti adolescenti affetti da rabdomiosarcoma (RMS) e trattati secondo i protocolli del soft tissue sarcoma commitee (STSC) (1).

Una seconda parte del Dottorato è stata dedicata all'analisi dei risultati ottenuti dai pazienti affetti da RMS trattati in seconda linea con il regime Topotecan/Carboplatino (2).

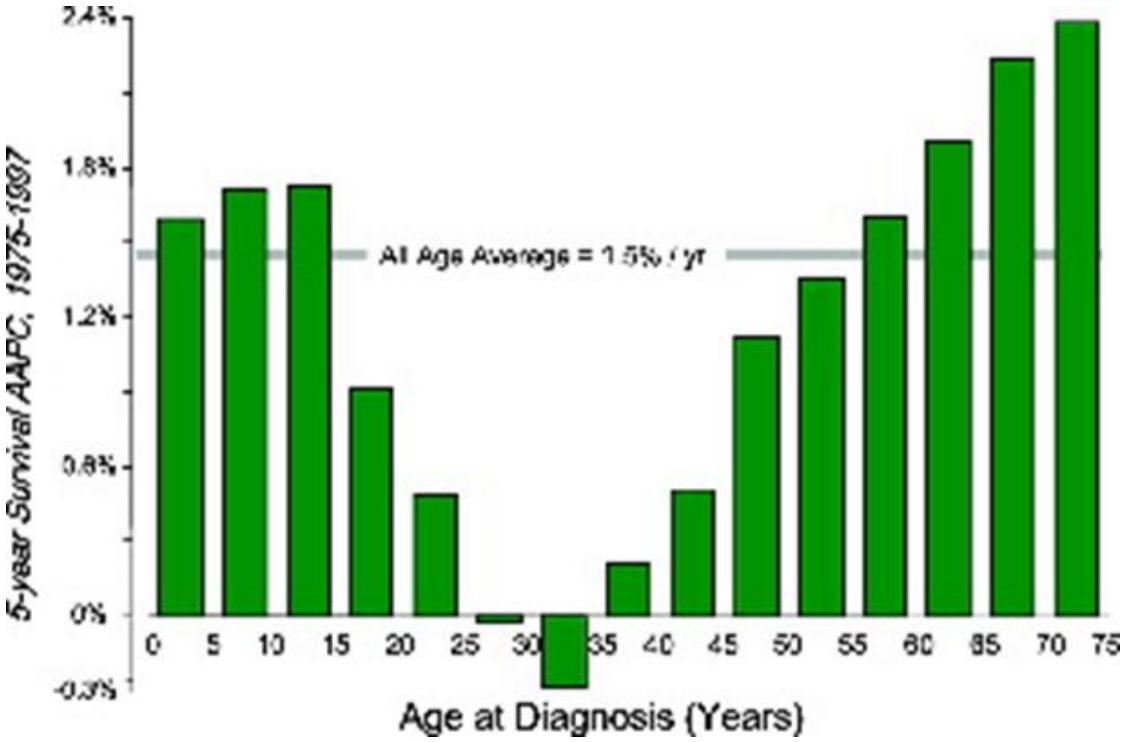
Fin dall'inizio dell'attività di Dottorato, visti gli obiettivi dello stesso, è iniziata una formazione specifica nell'ambito dei trials clinici, con partecipazione a corsi ad hoc, formazione di un gruppo di lavoro sui nuovi farmaci e apertura del nostro Centro a numerosi trials (3.2).

A "conclusione" di questo iter gli sforzi sono stati coordinati alla stesura di un protocollo di fase II per pazienti affetti da recidiva meningea di RMS/PNET. Il protocollo è in fase di stesura, verrà presentata l'attuale bozza (3.3).

1 GLI ADOLESCENTI

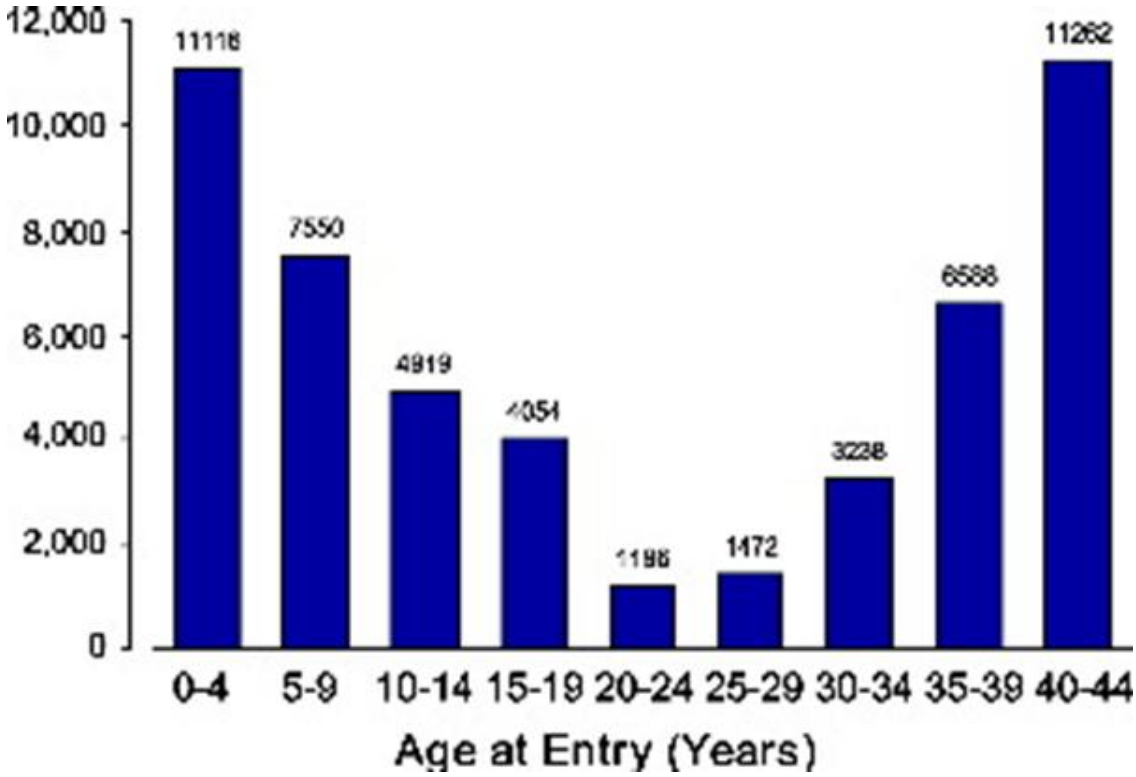
1.1 Introduzione

La Comunità Scientifica ha mostrato negli ultimi anni un crescente interesse per quella che viene definita "Adolescent and Young Adult Oncology" (AYA) (1). Dati epidemiologici delle ultime decadi mostrano per la fascia d'età 15-45 anni di pazienti oncologici i peggiori risultati in termini di outcome/sopravvivenza. L'analisi del SEER (Survival, Epidemiology and End Results) relativa ai dati di sopravvivenza da tumore in base all'età (1975-1997), ha mostrato un miglioramento annuale del tasso di sopravvivenza a 5 anni superiore all'1,5% per i pazienti di età <15 anni e >50 anni, a fronte di un tasso <0,5% tra i 15-24 anni, assenza di miglioramento tra i 24-35 anni (vedi grafico) (2, 3).

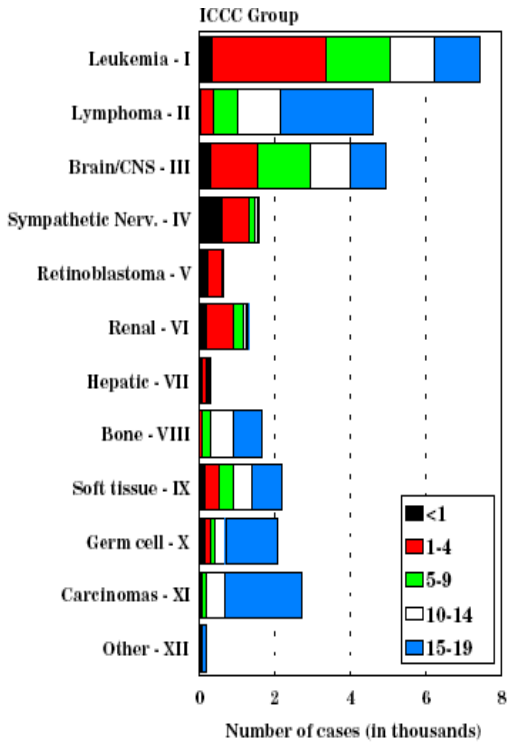


Tali risultati sono oggetto di ampio dibattito; uno dei principali fattori chiamati in causa a motivare questi pessimi risultati è la scarsa partecipazione dei pazienti adolescenti e

giovani adulti nei trials clinici; in effetti il tasso di arruolamento nei trials clinici in base all'età riflette l'andamento prognostico degli stessi pazienti (vedi grafico) (3, 4, 5, 6).



Altri fattori considerati importanti sono: una maggior aggressività biologica a parità di patologia (7, 8); ritardi diagnostici dovuti sia al paziente che ai professionisti della salute (il primo riluttante a esporre problematiche personali in una fase di maturazione complessa caratterizzata da senso di autonomia e "invincibilità", i secondi per scarsa consapevolezza/conoscenza delle patologie oncologiche di questa fascia d'età) (3, 9).
Questo gruppo di pazienti così complessi sia dal punto di vista sociale e psicologico che dal punto di vista dell'epidemiologia delle patologie oncologiche di cui sono affetti, risiedono in quella che viene definita un'area "grigia", "no-man's land", a metà strada tra l'Oncologia Pediatrica e l'Oncologia dell'adulto. Infatti in questo gruppo emerge una "transizione" epidemiologica: diminuiscono le patologie oncologiche pediatriche (Wilms, medulloblastomi, rabdomiosarcomi,…) e aumenta l'incidenza di quelle tipiche dell'età adulta (es. carcinomi), l'una di competenza pediatrica, l'altra dell'oncologo dell'adulto (vedi grafico).



Emerge pertanto la necessità di una sensibilizzazione della Comunità per evitare ritardi che aggravano la prognosi di questi pazienti, aumentare il tasso di arruolamento nei trials clinici (eventualmente alzando l'età limite dei protocolli pediatrici), ma soprattutto risulta fondamentale la stretta collaborazione tra gli Oncologi dell'adulto e del bambino.
Il nostro Centro sta via via rafforzando la gestione comune di questi pazienti, con partecipazione degli Oncologi dell'adulto a demand ai multidisciplinari settimanali del gruppo sarcomi parti molli/tumori solidi pediatrici e viceversa, allo scopo di potenziare una gestione veramente multidisciplinare del paziente adolescente/giovane adulto con patologia pediatrica e del paziente pediatrico con patologia dell'adulto.
La peculiarità e l'interesse crescente per l'argomento ci ha spinti a condurre uno studio su una popolazione di pazienti pediatrici e adolescenti affetti da rabdomiosarcoma trattati secondo i protocolli del STSC.
I risultati dello studio (reso possibile dalla collaborazione con i maggiori Centri italiani di Oncologia pediatrica) sono stati oggetto di presentazioni a Congressi e i dati sono stati pubblicati su *Cancer. 2012 Feb 1;118(3):821-7. Rhabdomyosarcoma in adolescents: a report from the AIEOP Soft Tissue Sarcoma Committee. Bisogno G, Compostella A, Ferrari A, Pastore G, Cecchetto G, Garaventa A, Indolfi P, De Sio L, Carli M.*

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1.2 Rhabdomyosarcoma in Adolescents. A Report From the AIEOP Soft Tissue Sarcoma Committee

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BACKGROUND: In many types of cancer, the survival rates are reported to be less favorable for adolescents compared with younger children. To investigate whether this is true for adolescents with rhabdomyosarcoma (RMS), the results obtained in patients enrolled in protocols run by the Italian Soft Tissue Sarcoma Committee (STSC) were analyzed. METHODS: From 1988 through 2005, 643 patients were registered (567 children ages birth-14 years and 76 adolescents ages 15-19 years) and treated in 4 STSC protocols. The number of patients enrolled was compared with the expected number calculated from incidence rates derived from the Italian network of cancer registries. RESULTS: Only 27% of the expected number of adolescents with RMS were enrolled in the STSC trials. Compared with children, adolescents were found to have a longer interval from initial symptoms to diagnosis (8 weeks vs 4.6 weeks), more alveolar RMS (47.4% vs 32.6%), lymph node infiltration (39.1% vs 23.3%), and metastases at the time of diagnosis (30.7% vs 17.8%). The 2 age groups received similar treatments. The 5-year overall survival (OS) rate was 68.9% in children versus 57.2% in adolescents (P: 0.006), and the progression-free survival (PFS) rate was 64.3% in children versus 48.1% in adolescents (P: 0.0237). On multivariate analysis, age, tumor site, lymph node involvement, and metastases were found to be significant prognostic factors for OS and PFS. CONCLUSIONS: Survival for adolescents with RMS enrolled in STSC protocols appears to be satisfactory. The higher prevalence of unfavorable tumor characteristics noted among adolescents seems to explain their worse outcome compared with children. However, the limited number of adolescents enrolled in STSC studies is worrisome, and cooperation with oncologists who treat adults needs to be improved.
Cancer 2011;000:000–000. VC 2011 American Cancer Society.

KEYWORDS: rhabdomyosarcoma, adolescents, soft tissue sarcoma, survival.

Rhabdomyosarcoma (RMS) is a rare tumor that typically affects children and adolescents, with an annual incidence of 4.3 cases per 1 million population aged <20 years. Approximately 3 in 4 cases occur in children aged <10 years, with a peak incidence between ages 3 and 5 years and a second, smaller peak in adolescence, after which the incidence drops significantly with increasing age. Approximately 70% of patients with localized RMS can now be cured, but their outcome is influenced by various prognostic factors identified over the years and currently used for risk stratification and risk-adapted treatment decisions (1). Along with other variables such as histology, local and distant invasiveness, and tumor site and size, the patient's age has emerged as one of the most relevant factors, with older patients reported to have a worse prognosis (2,3).

Among the various age groups, adolescents with cancer form a group with particular features. Several studies have shown that improvements in the survival rates achieved in recent years have been less satisfactory for adolescents and young adults compared with younger children (4,5). Among the reasons suggested to explain this phenomenon are the greater presence in adolescents of tumors with less favorable characteristics, delays in the diagnosis, and a low accrual of adolescents in clinical trials (5,6).

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To the best of our knowledge, no published studies to date have focused on adolescents with RMS. Therefore, we analyzed the clinical and demographic characteristics, treatment, and outcome for patients in this age group who were treated in the clinical trials coordinated by the Associazione Italiana di Ematooncologia Pediatrica (AIEOP) Soft Tissue Sarcoma Committee (STSC) between 1988 and 2005. Because age was not considered to be a factor for treatment stratification purposes, children and adolescents received the same treatment, making them an ideal population for evaluating the relative contributions of the above-mentioned factors.

To our knowledge, no other multicenter or institutional protocols including adolescents, or even adults, with RMS were being run in parallel in Italy during the same period of time.

MATERIALS AND METHODS

Over the course of 18 years, patients were enrolled by AIEOP centers in 4 consecutive protocols: RMS-88 and RMS-96 for children and adolescents with localized RMS, and MMT4 and RMS4.99 for those with metastatic disease. Pretreated patients, patients with RMS as a second malignancy, or though for which no data were available were not considered eligible for the purpose of this analysis. Patients ages 15 years to 19 years were classified as adolescents, and those aged <15 years were classified as children.

Details regarding surgery, radiotherapy, and chemotherapy had been collected prospectively and were reviewed for the purpose of the current study. Informed consent according to the local institutional guidelines was obtained at the time of a patient's enrollment in each protocol.

Disease was staged according to the TNM and Intergroup Rhabdomyosarcoma Study (IRS) systems. In the TNM system, T1 indicates tumors confined to the organ or tissue of origin and T2 lesions invade contiguous structures; T1 and T2 are further classified as A or B according to whether the tumor diameter is < 5 cm or > 5 cm, respectively. N1 indicates regional lymph node involvement. In the IRS system, group I defines completely excised tumors, group II indicates macroscopically resected tumors with microscopic residual disease and/or regional lymph node involvement, group III indicates macroscopic residual disease after incomplete resection or biopsy, and group IV is used to denote metastatic disease.

Despite differences in the chemotherapy regimens used in the various protocols, the policy dictating the therapeutic decisions remained much the same over the years. Treatment was based on: 1) conservative surgery or biopsy at the time of diagnosis; 2) initial chemotherapy according to various regimens; 3) disease evaluation after the first 3 or 4 courses of chemotherapy; 4) second-look surgery in the event of residual disease; and 5) adjuvant chemotherapy after initial or delayed radical surgery. Radiotherapy was used for patients considered to be at risk of developing local recurrence (IRS groups II, III, and IV).

Various chemotherapeutic regimens were adopted over the years, based on the different protocols and the extent of disease. Briefly, in the RMS-88 study, vincristine and actinomycin D (VA regimen) were administered to patients in IRS group I, ifosfamide was added for patients in IRS group II (IVA), and doxorubicin (adriamycin) (VAIA) was added for patients in IRS group III. In the RMS-96 protocols, low-risk patients were treated with VA, standard-risk patients received IVA, and high-risk patients were randomized to receive either the VAIA or CEVAIE (carboplatin, epirubicin, vincristine, etoposide, ifosfamide, and actinomycin D) combinations; details of the chemotherapy regimens have been published elsewhere (7).

Patients included in the MMT4 protocol received 4 cycles of the CEVAIE regimen. In 1991, the protocol was amended and the fourth cycle was replaced with high-dose melphalan (200 mg/m2) with autologous peripheral blood stem cell rescue (8). Finally, in the RMS4.99 protocol, after the initial CEVAIE regimen, 3 consecutive cycles of high-dose chemotherapy were administered, followed by local treatment and maintenance chemotherapy with vincristine, actinomycin D, and cyclophosphamide (9).

Response was formally evaluated after initial chemotherapy (week 9) and at the end of treatment and was defined as complete response (CR; clinically or histologically confirmed complete disappearance of disease); partial response (PR; at least a two-thirds reduction in tumor volume); minor response (a greater than one-third but less than two-thirds reduction in tumor volume); no response or stable disease, or a less than one-third reduction in tumor volume; and progressive disease (an increase in tumor size or the detection of new lesions).

Patient Accrual

The number of patients enrolled in the AIEOP protocols was compared with the number of cases expected to be diagnosed in Italy during the same period, based on incidence

data from the well-established Italian network of population-based cancer registries (AIRTUM), which pools data drawn from 22 general registries and 3 specialist registries (2 regarding childhood and adolescent cancer and 1 pertaining to female breast cancer) and covers 32.9% of children and 26.9% of adolescents residing in Italy (10).

Statistical Analysis

Survival curves were calculated using the Kaplan-Meier method. Overall survival (OS) was considered as the time from diagnosis to last follow-up or death because of any cause and progression-free survival (PFS) was considered as the time from diagnosis to first disease progression, recurrence, death because of any cause, or latest contact for children who never experienced an event. The logrank test was used to compare survival rates between different subgroups of patients by univariate analysis, considering patient characteristics (age and gender) and tumor features (histological subtype, site, size, invasiveness, lymph node involvement, and type and number of metastases). The different sites were grouped by prognosis as favorable (orbit, head and neck, and genitourinary non bladder/prostate) or unfavorable (parameningeal, extremities, bladder/prostate, and other sites). A P value <.05 was considered statistically significant. A multivariate analysis was conducted with the Cox proportional hazards regression method to determine the independent prognostic influence of pretreatment factors on survival, using the variables found to correlate with OS and PFS on univariate analysis. The study was approved by the Ethics Committees of all the centers taking part and informed consent was obtained from all patients enrolled in the protocols.

RESULTS

Patients

The clinical characteristics of the 643 patients considered for this analysis are shown in Table 1.

A total of 567 patients were children (median age, 4.8 years) and 76 were adolescents (median age, 16.5 years). The male/ female ratio was 1.5 in children and 2.3 in adolescents.

A median of 4 adolescents (range, 1-8 adolescents) were registered each year during the study period, whereas 15.4 adolescent cases per year were expected according to the AIRTUM data (10). The observed-to-expected (O/E) ratio for adolescents with RMS was 0.27, whereas that for children was 0.9 during the same period. The number of adolescents registered for the STSC protocols increased progressively from 3.6 (1988-1993) to 5.5 (2000-2005) cases per year.

Data regarding the time elapsed between the onset of symptoms and diagnosis were available for 580 patients and ranged from 0 to 155 weeks (median, 5 weeks). The median diagnostic delay for children was 4.6 weeks (range, 0 weeks-155 weeks), which differed significantly ($P < .0001$) from the findings among adolescents, whose median latency period was 8 weeks (range, 0 weeks-74 weeks).

The tumor characteristics differed in the 2 age groups. Adolescents had more cases of genitourinary non bladder/prostate tumors (36.8% vs 12.9% in children; $P < .0001$), alveolar histology (47.4% vs 32.6% in children; $P = .01$), lymph node involvement (35.5% vs 21.7% in children; $P = .004$), and metastases at the time of diagnosis (30.3% vs 17.8% in children; $P = .008$) (Table 1).

Treatment

Patients were treated with a combined approach including surgery, radiotherapy, and chemotherapy. Overall, 358 patients underwent tumor resection at the time of diagnosis or after chemotherapy (313 children and 45 adolescents). Surgery was complete in 45% and 44.4% of cases, respectively. The high rate of complete resections performed at the time of diagnosis (IRS group I) among the adolescents is explained by a large number of patients with paratesticular tumors in this age group.

Data regarding radiotherapy were available for 598 patients. The percentage of patients treated with radiation was similar in the 2 age groups (61.6% in children and 59.4% in adolescents). There were no differences with regard to the doses administered, with the median dosage being 44.8 gray (Gy) (range, 14.4-69.0 Gy) for children and adolescents alike.

The response to initial chemotherapy was evaluable in 438 patients and was good (CR + PR) in 74.3% of children and 81.1% of adolescents. Adolescents had a higher, although not statistically significant ($P = .4$), rate of tumor progression during the course of treatment (5.4% vs 2.9% in children).

Survival

With a median follow-up of 8.8 years (range, 3 years-20.5 years), the 5-year OS rate was 68.9% for children and 57.2% for adolescents (P = 0.006), and the 5-year PFS rate was 64.3% and 48.1%, respectively (P = .02) (Fig. 1).

Table 1. Clinical Characteristics of the Patients

Characteristic	Children	%	Adolescent	%	Total
Male	337	5	53	6	390
Female	230	4	23	3	253
Primary site					
Orbit	56	9	2	2	58
Head and neck	57	1	9	1	66
Parameningeal	106	1	10	1	116
GU BP	57	1	5	6	62
GU NON-BP	73	1	28	3	101
Extremities	84	1	9	1	93
Other sites	134	2	13	1	147
Histology					
Alveolar	185	3	36	4	221
Non alveolar	374	6	39	5	413
NOS	8	1	1	1	9
T					
T1	262	4	36	4	298
T2	296	5	36	4	332
Missing	9	1	4	5	13
N					
N0	405	7	42	5	447
N1	123	2	27	3	150
Missing	39	6	7	9	46
Tumor size					
<5	243	4	32	4	275
>5	305	5	39	5	344
Missing	19	3	5	6	24
IRS group					
I	65	1	20	2	85
II	72	1	7	9	79
III	329	5	25	3	354
IV	101	1	23	3	124
Missing	—		1	1	1

Abbreviations: GU BP, genitourinary bladder/prostate; GU NON-BP, genitourinary non-bladder/prostate; IRS, Intergroup Rhabdomyosarcoma Study; NOS, not otherwise specified.

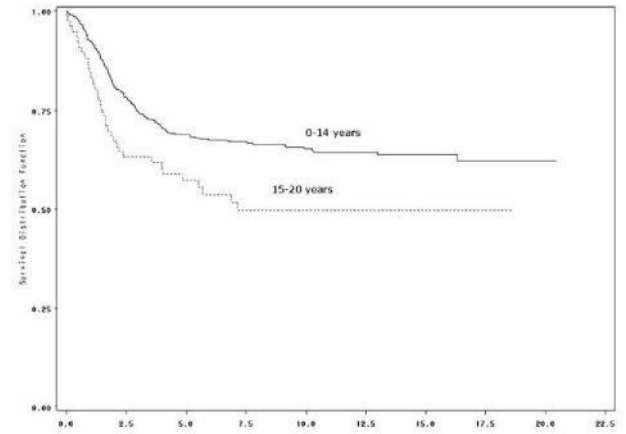
When patients with localized disease were considered alone, the results were similar in children and adolescents, with 5-year OS rates of 76.6% versus 78.6% and 5-year PFS

rates of 72.5% versus 66.8%, respectively (P: 0.9162). Patients with metastatic disease at the time of diagnosis fared much worse, with the OS and PFS rates dropping to 31.8% and 24.6%, respectively, for children, and 10.4% and 5.8%, respectively, for adolescents (P: 0.01).

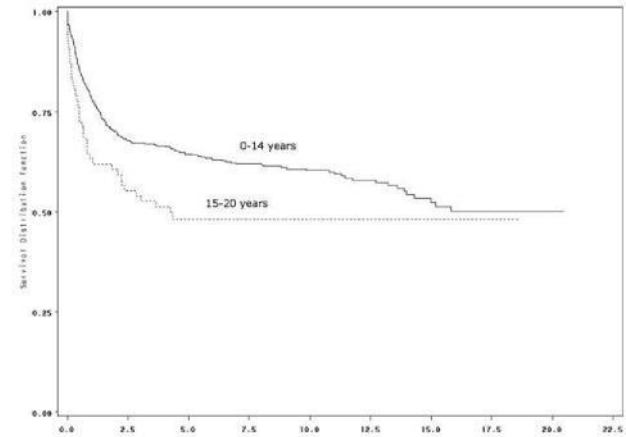
Multivariate analysis identified several factors that were independently and significantly correlated with better survival: age < 15 years, favorable tumor sites, and no lymph node or metastatic dissemination (Table 2). All these variables also were confirmed to be independent prognostic factors for PFS.

Because previous studies found age to be significant using 1 year and 10 years of age as the lower and upper cutoff values, we performed a further analysis for these 2 age groups. The survival rate was much the same in children ages 10 years to 14 years and adolescents, and was worse than in younger children (Fig. 2). The 5-year OS and PFS rates were significantly higher in children ages 1 year to 9 years compared with children ages 10 years to 19 years: 72% versus 56.8%, respectively, (P < .0001) and 64% versus 52%, respectively (P: 0.003).

A new multivariate analysis in which different age groups were taken into account (age < 1 year, ages 1year-9 years, and ages 10 years-19 years) produced similar results, with age (1 year-9 years), favorable tumor sites, and the absence of lymph node or metastatic dissemination found to be independently associated with better OS and PFS.



Age groups	No. of subjects	Events	5-year survival (95% CI)	p
0 - 15	567	187	68.89 (64.79 - 72.61)	0,006
15 - 20	76	36	57.21 (45.15 - 67.56)	



Age groups	No. of subjects	Events	5-year progression free survival (95% CI)	p
0 - 15	567	228	64.3 (60.1-68.1)	0,02
15 - 20	76	39	48.1 (36.4-58.9)	

Figure 1. (Top) Overall survival and (Bottom) progression free survival are shown in children and adolescents with rhabdomyosarcoma. 95% CI indicates 95% confidence interval.

DISCUSSION

Despite several reports suggesting that the survival trends for adolescents with cancer are not improving to the same degree as in children (4,5), to our knowledge there have still been few studies published to date regarding this particular population, and none focusing on RMS.

The STSC protocols did not differentiate treatment by age; in particular, there were no differences with regard to the local treatment strategies and similar percentages of children and adolescents underwent surgery and radiotherapy.

In our analysis, the survival results were better for children. Various reasons have been suggested to explain why adolescents may fare less well than children with the same disease, and one of the most important may be a higher incidence of adverse prognostic factors in older patients. Our data confirm this aspect in patients with RMS; unfavorable tumor characteristics (eg, alveolar subtype, lymph node involvement, and metastases at the time of diagnosis) were more common in adolescents than in children. An unexpectedly high number of adolescents with paratesticular tumors were registered in the STSC protocols, possibly reflecting a more effective referral to AIEOP centers by urologists and surgeons. The paratesticular site is highly favorable and explains why adolescents had a higher percentage of complete tumor resections at the time of diagnosis; this may also have contributed to raising the PFS and OS in the adolescent age group.

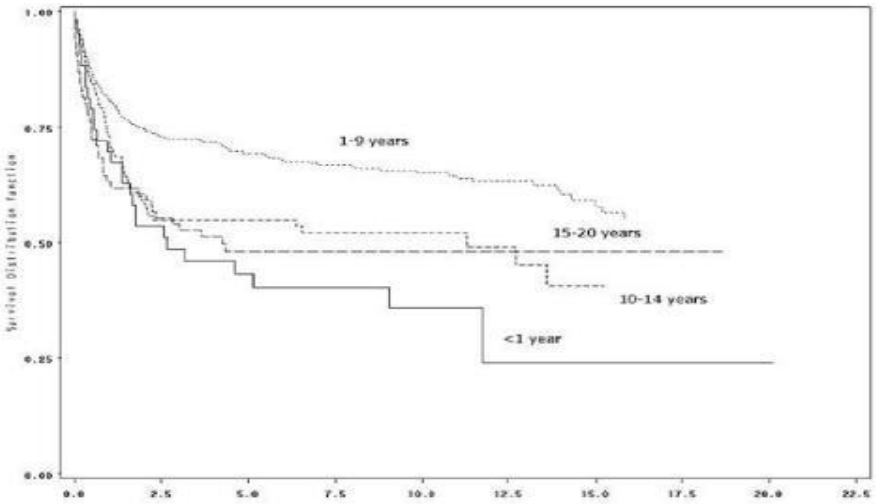
Age per se has been indicated as a prognostic factor in various tumors, including RMS (11,12). Joshi et al analyzed the clinical features and treatment outcome of patients aged < 21 years in the IRS group protocols and concluded that a larger percentage of patients aged > 10 years have an alveolar histology, unfavorable tumor sites, and a more advanced tumor stage than noted in children aged < 10 years, but all these features were not enough to justify their worse outcome, and age remained a strong independent risk factor (2). More recently, age (> 10 years and < 1 year) proved to be an adverse prognostic factor in a pooled analysis of 788 patients with metastatic RMS (3). In the current study, which included patients with localized and metastatic RMS, unfavorable tumor features and advanced stage in particular appeared to have a more important role, with the role of age diminishing only when localized tumor was considered separately. The outcome was very similar for the patients ages 10 years to 14 years and those ages 14 years to 19 years, suggesting that the age cutoff of 10 years may be more appropriate for the purpose of attributing different risk factors. The results of the current study thus indicate that adolescents should not be treated differently from younger children on the basis of age alone.

Some authors have suggested that drug metabolism or treatment-related toxicity might differ between adolescent and younger patients, potentially explaining the difference in outcome (13). The limited number of major toxic events recorded in the population analyzed in the current study prevented us from investigating this aspect.

Table 2. Five-Year Overall Survival by Prognostic Factor (Multivariate Analysis)

Factor	Patients	Events	HR (95% CI)	P
Age, y	567	187	1a	.0146
	76	36	1.67 (1.11-2.52)	
Tumor site	225	38	1a	.0007
	418	185	1.98 (1.33-2.93)	
Lymph node involvement	447	109	1a	<.0001
	150	91	1.95 (1.41-2.69)	
IRS group	85	3	1a	<.0001
	79	18	5.39 (1.56-18.59)	
	354	114	6.37 (1.96-20.74)	
	124	87	17.10 (5.08-	

Abbreviations: 95% CI, 95% confidence interval; HR, hazard ratio; IRS, Intergroup Rhabdomyosarcoma Study. a Reference category.



Age groups	No. of subjects	Events	5-year progression free survival (95% CI)	p
< 1	43	27	43.2 (28.0-57.5)	<0.0001
1-10	408	144	69.2 (64.4-73.5)	
10-15	116	57	54.8 (45.2-63.3)	0,02
15 - 19	76	39	48.2 (36.5-58.9)	

Figure 2. Progression-free survival is shown by age group. 95% CI indicates 95% confidence interval.

However, it is important to improve our knowledge in this area by planning clinical pharmacology studies in these patients.

Another particular factor that is apparent in the adolescent population is the diagnostic delay. Several authors have suggested that the time elapsing from the onset of symptoms to diagnosis is longer for adolescents than for children (6,14). This was confirmed in the population in the current study, in whom the median diagnostic delay for adolescents was nearly twice as long as that for children (8.4 weeks vs 4.8 weeks), and suggests that the more advanced stage of disease noted in adolescents, and the consequently worse prognosis, may be partially explained by a late diagnosis. The reasons for this diagnostic delay lie within the limited awareness of families and the community that adolescents can develop cancer and in the fact that adolescents tend to have a strong sense of independence and may be reluctant to ask for help or submit to a medical examination, and therefore symptoms are often attributed to physical exertion, fatigue, trauma, and stress.

An important issue that most likely interferes with any improvement being made in the survival of adolescents concerns their limited participation in clinical trials (5,15). When survival rates and accrual rates were compared using Surveillance, Epidemiology, and End Results (SEER) data, an overlap became apparent: the lower the

accrual rate, the worse the results in terms of survival (16). To our knowledge, the protocols coordinated by the STSC were the only national multicenter protocols available for children with RMS in Italy, and should be considered a type of standard of treatment. Only 27% of the expected number of adolescents was recruited into the STSC protocols, however, whereas > 90% of the expected numbers of children were enrolled in these protocols during the same period. This poor recruitment of adolescents in pediatric protocols has been highlighted by a recent analysis comparing the number of cases registered at the AIEOP centers with the incidence rates obtained from the AIRTUM population-based registries by cancer type. The O/E ratio for RMS was 0.33, which is one of the highest among all cancer types in adolescents but grossly unsatisfactory (10). This demonstrates that adolescents in Italy are often referred to adult oncology units although their disease is a "pediatric" cancer. Programs dedicated to adolescents and young adults are still limited and adolescents with RMS may consequently receive treatment according not to current pediatric guidelines but to the approach adopted for adult soft tissue sarcoma, which may make their survival rates less satisfactory, as shown by the analysis of a series of adult patients with RMS (17).

CONCLUSIONS

The survival of children and adolescents enrolled in STSC protocols could be considered to be satisfactory, especially in patients without metastases. The results of the current study indicate that RMS presents with more aggressive features in adolescents and this has a major impact on their survival. An additional factor concerns the finding that only a small percentage of the adolescents affected are enrolled in clinical trials, and this may prevent them from receiving the best possible care. A better cooperation with oncologists who treat adults is mandatory to improve the treatment of adolescents with RMS.

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The authors made no disclosures.

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2 ANALISI DATI TOPOTECAN/CARBOPLATINO

2.1 Introduzione

Il RMS è il più comune sarcoma delle parti molli nella popolazione pediatrica e adolescente; nelle ultime decadi l'affinamento dell'approccio multimodale alla patologia, costituito da chirurgia, radioterapia (RT) e polichemioterapia (CT), ha permesso di migliorare moltissimo la prognosi dei pazienti pediatrici affetti da questa neoplasia, passando da una sopravvivenza a 5 anni del 50% negli anni '70 al 70% degli anni '90 (1). Circa il 90% dei pazienti con malattia localizzata all'esordio ottiene una remissione completa; tuttavia 1/3 di pazienti ricade (2, 3). Per questi pazienti (metastatici, refrattari, recidivi), la prognosi è ancora ad oggi infausta (4).

Sono quindi necessari nuovi farmaci e nuove strategie terapeutiche per migliorarne la prognosi.

Risulta di fondamentale importanza identificare fattori prognostici utili a disegnare protocolli "risk-based". Un recente studio ha dimostrato che l'istologia, la sede, il tipo e il timing della recidiva sono fattori correlati alla prognosi in modo significativo (5).

Tra i vari farmaci identificati come attivi in studi preclinici e di fase I vi sono i derivati delle Camptotecine, Irinotecan e Topotecan. Si tratta di molecole che inibendo la Topoisomerasi I interferiscono con la divisione cellulare e la replicazione del DNA.

Entrambe le molecole hanno dimostrato in studi preclinici attività su linee cellulari di numerosi tumori pediatrici, un buon profilo di tossicità nonché efficacia in studi di fase I (6, 7, 8, 9), anche sui RMS (10, 11).

Vista l'attività delle singole molecole, successivamente sono state studiate varie combinazioni: Topotecan+ciclofosfamide (12, 13), Topotecan alternato allo schema VAC (14), Topotecan+Vincristina e Doxorubicina (15, 16)

Da tali studi emerge che questi farmaci, pur non impattando in modo eclatante sulla sopravvivenza, permettono di ottenere un discreto tasso di riposta in pazienti spesso pesantemente pretrattati; vengono quindi attualmente considerati delle opzioni terapeutiche potenzialmente valide.

L'attuale Protocollo per il trattamento del RMS (EpSSG 2005) propone in seconda linea una strategia terapeutica basata su un regime con Topotecan e Carboplatino. Pazienti che non rispondono in maniera soddisfacente ai primi 3 cicli di CT dimostrano una

cattiva prognosi e sono considerati “refrattari”; pertanto vengono shiftati ad un trattamento che prevede l’utilizzo di farmaci non utilizzati fino ad allora (Topotecan, Carboplatino, Ciclofosfamide ed Etoposide; l’antraciclina viene utilizzata nei pazienti in cui non era prevista in prima linea). Stesso dicasi per i pazienti che ricadono dopo il termine della CT di prima linea.

Del Topotecan si è detto sopra; il razionale per l’utilizzo del Carboplatino in questo setting si basa sul precedente impiego dello stesso in regimi polichemioterapici riconosciuti attivi nel RMS quali il CEVAIE. Carboplatino è stato poi usato da solo in un “window study” dal UKCCSG nonchè in uno del CWS per i RMS metastatici. La fattibilità della combinazione è stata provata in occasione di uno studio di fase II eseguito al Bambin Gesu’ di Roma.

Un’analisi preliminare dei risultati ottenuti nei pazienti affetti da RMS recidivo o refrattario trattati con Topotecan e Carboplatino, ha confermato la fattibilità della combinazione: la tossicità è risultata lieve e prevalentemente ematologica; il tasso di risposta discreto, comparabile con quello osservato con altre combinazioni.

Su tale base è stato condotto uno studio prospettico multicentrico su pazienti affetti da RMS refrattario/recidivo trattati in seconda linea con il regime Topotecan/Carboplatino.

Lo scopo dello studio era analizzare le caratteristiche delle recidive, il profilo di tossicità e l’efficacia della combinazione Topotecan/Carboplatino.

Segue l’articolo che a breve sarà sottomesso a rivista scientifica.

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2.2 A Topotecan/Carboplatin based strategy for children with refractory or recurrent rhabdomyosarcoma

Alessia Compostella, MD1, Gianni Bisogno, MD, PhD1 et al.

ABSTRACT

The prognosis for children with resistant/relapsing Rhabdomyosarcoma (RMS) remains poor and therefore there is a need to test new drugs combinations. Topotecan (T) and Carboplatin (C) are known to have activity against a variety of pediatric tumors so a T/C based chemotherapy has been proposed as second line chemotherapy for children relapsed after being treated in the soft tissue sarcoma committee (STSC) protocols.

Methods:

38 patients with available data on response have been analyzed: 8 resistant to first line treatment and 30 treated at relapse. Treatment: T: 2 mg/m2 days 1,2,3; C: 250 mg/m2 days 4,5 every 3 weeks. Tumor response has been evaluated after 2 cycles adopting standard criteria: complete response (CR); partial response (PR= tumor size reduction >50%); minor response (MR= reduction <50%); no response (NR= reduction <25%), progressive disease (PD= increase of tumor size or detection of new lesions)

Results:

18 patients presented unfavorable histotype and 19 a favorable one (1 NOS). At diagnosis IRS Group was: II: 3 patient; III: 25; IV: 10. Tumor site was unfavorable in the great majority of children (30/38): 9 parameningeal (PM), 9 extremities, 9 other sites, 3 genitorurinary bladder-prostate (GU-BP); among 8 favorable sites 4 were head and neck non parameningeal, 3 genito-urinary non BP, only 1 orbit. 24 patients received 2 cycles, 3 only 1 due to early PD. Toxicity was predominantly hematologic with no severe non-hematologic toxic events reported. Major response was evident in 9 patients (CR+PR). The response rate was globally 28%; 15% in favorable histology and 33% in unfavorable one.

Conclusions:

Our study shows that the T/C combination has a mild toxicity in pretreated patients. The response rate is somewhat lower when compared to other combinations tested in phase II studies but it is of interest for the population with alveolar subtype.

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INTRODUCTION

Despite the success of current multimodal therapy which has increased the survival of patients with RMS over 70% there is still a substantial number of patients who relapse and need effective salvage chemotherapy. Thus it is important to investigate novel antineoplastic combinations for their potential incorporation into front line therapy.

In this study we tested a chemotherapy strategy based on the administration of regimens including Topotecan (T) and Carboplatin (C) in a group of children and adolescents with refractory RMS.

Topotecan, a campthotecine derivative, has demonstrated in pre-clinical studies high activity against pediatric malignancies such as medulloblastoma, neuroblastoma and rhabdomyosarcoma. Consequently several studies of T alone or in association with other antiblastic drugs were initiated.

Carboplatin has been part of previously used regimens (CEVAIE) that proved to be effective against RMS (1). It has also been used alone in a window study conducted by the UKCCSG. A phase II trial has been performed at the Bambino Gesù Hospital in Rome showing the feasibility of the proposed regimen. The T/C combination is also used as window treatment in the current CWS protocol for metastatic RMS.

This two drugs have constituted the base of the second line strategy recommended for children with RMS who relapsed after being treated in the STSC protocols.

MATERIAL AND METHODS

Between 2002 (only one patient was diagnosed in 1995) and 2011, 38 patients under 19 years old joined this study. They were registered from 12 centers belonging to the AIEOP (Associazione Italiana di Ematologia e Oncologia Pediatrica) and taking part in studies coordinated by the AIEOP STSC.

Eligible patients were required to have a histologically-confirmed diagnosis of RMS, and to be refractory or relapsing after the inclusion in one of the protocols coordinated by the STSC.

Other eligibility criteria were: a life expectancy of at least 8 weeks, a modified Lansky score of > 50, recovery from the toxic effects of prior chemotherapy, a hemoglobin level greater than 9 g/dl, an absolute neutrophil count greater than 1,500/mm3, a platelet count higher than 100,000/mm3, adequate liver function (bilirubin level ≤ 1.5 mg/100

ml; ALT ≤ twice the normal value), adequate renal function (serum creatinine concentration ≤ 1.5 mg/dL or creatinine clearance > 60 ml/min/1.73 m2) and normal metabolic parameters (serum electrolytes, glucose, calcium, phosphorus). Patients with an interval of less than 3 weeks since the administration of radiotherapy or chemotherapy were excluded.

At the baseline, the tumor was reassessed, with computed tomography (CT) or a magnetic resonance imaging (MRI) scans of disease sites and measurements of all disease parameters, chest X-ray, chest CT scan, whole body technetium bone scan and bone marrow aspirates and biopsies.

The study was approved by the Ethics Committees of each center taking part and informed consent was obtained from patients or parents, as appropriate.

Treatment

Patients received 2 blocks of T\C, followed by alternating blocks of Topotecan \ Cyclophosphamide and Carboplatin \ Etoposide for a total of 6 courses with 3-week interval (see figure 1).

Local treatment was scheduled after the two initial courses. Surgery and radiotherapy had to be considered but the type and time of local treatment were left to the responsible clinician according to the patient condition, relapsing tumor characteristics, and previous treatment. The coordinating STSC Centre was available to discuss the strategy for the most difficult cases.

The schedule for drugs administration is described in figure 1 and was as follow: Topotecan: 2 mg/m2/day administered by 30 minutes intravenous infusion once daily on day 1, 2 and 3 (total dose 6 mg/m2/course); Carboplatin: 250 mg/m2/day in 1 hour intravenous infusion on day 4 and 5 (total dose 500 mg/m2 course).

Cycles were given every 21 days, with neutrophils >1.0 x 109/l and platelets to >80 x 109/l and following resolution of non-hematopoietic toxicity. Use of colony-stimulating factors were given according to Institutional policy.

Toxicity was graded using the National Cancer Institute Common Toxicity Criteria version 2.0.

Response evaluation

After the initial two T/C courses and at the end of treatment, a formal assessment of the primary tumor and all sites of metastases had to be performed.

Response criteria were as follows: complete response (CR) = resolution of all evidence of disease; partial response (PR) = a tumor size reduction of more than 50% in the sum of the products of the two maximum perpendicular diameters of all measurable lesions; minor response (MR) = a reduction of less than 50% but more than 25% in the sum of the products of the two maximum perpendicular diameters of all measurable lesions. Stable disease or a reduction in size of less than 25% was recorded as no response (NR), while an increase in tumor size or the detection of new lesions was considered as progressive disease (PD). Responses had to last at least 4 weeks after the assessment of the response.

Due to the difficulty in judging tumor response on bone marrow aspirates, we decided not to consider the bone marrow in the assessment of tumor response unless there was clear evidence of progressive disease or a new lesion.

Statistical method

Survival curves were calculated using the Kaplan-Meier method, considering: overall survival (OS), from the dates of relapse to latest follow-up or death from any cause; progression-free survival (PFS), from diagnosis to first progression, relapse, death from any cause or latest contact for children who never experienced an event.

The log-rank test was used to compare survival rates between different subgroups of patients in univariate analysis, considering patients' characteristics (age and gender) and tumor features (histological subtype, site, size, invasiveness, lymph node involvement, type and number of metastases). The different sites were grouped according their prognosis in favorable (orbit, head and neck, genitor-urinary non bladder prostate) and unfavorable (parameningeal, extremities, bladder-prostate, other sites). A p-value of less than 0.05 was considered statistically significant. A multivariate analysis was conducted using Cox's proportional hazards regression method to determine the independent prognostic influence of pretreatment factors on survival, using the variables correlated with OS and PFS at univariate analysis.

A phase II methodology using a Gehan 2-step design has been applied to evaluate the response to the two initial T/C cycles. The expected effectiveness (□) was considered as 20% for the whole group. If at least one response was recorded in the first 14 eligible patients, recruitment was to continue to at least 25 patients so that the standard error of the observed response rate would be □0.10.

The study was approved by the Ethics Committees of all centers taking part and informed consent was obtained for all patients enrolled on the protocol.

RESULTS

Clinical features

A total of 38 patients joined the study, 32 of whom were evaluable for response to the T/C response study. Patients characteristics are shown in table 1. The age range was 0.4 – 18.6 years (median 4.7; media 6.2). 16 were male, 22 were female. Histotypes were: 18 were unfavorable RMS, 20 favorable (18 embrional RMS, 1 spindle cell RMS, 1 NOS RMS). Tumors were mainly located in unfavorable sites. 10 patients were metastatic at diagnosis. At the entry in the study 8 patients had persistent disease at the end of first-line treatment, 20 had a loco-regional relapse (15 only local, 1 with concomitant lymph node involvement, 4 only node involvement), the others had only distant relapse or local and distant relapse.

Treatment

Patients had been previously treated in 12 italian hemato-oncology units according to different protocols named RMS88, RMS4.99, RMS96, EpSSG2005. Surgery has been performed in all patients at diagnosis, nearly all (35) being diagnostic biopsies; 10 patients underwent surgery after initial chemotherapy. Radiotherapy was delivered to 23 patients during first line chemotherapy (CT); 15 did not (8 of them because of age). First line CT included high-dose chemotherapy with stem cell rescue in 2 patients.

Local treatment was scheduled after the two initial T/C courses: 8 patients underwent surgery; 2 of them being microscopically radical, 3 macroscopically radical, a patient suffer a mutilating operation (exenteratio orbitae), 2 had no data about. Radiotherapy was delivered to 20 patients, 12 of them had been irradiated during first line chemotherapy, 8 were not (4 because of young age).

After T/C CT many patients were treated with alternating Topotecan/Cyclofosphamide-Etoposide/Carboplatin courses till progression. Other drugs frequently used were low dose Vinorelbine and Cyclophosphamide. Some patients have been treated with poliCT: VAC, ICE, Gemox; drugs less used were Irinotecan, Vincristine, Temozolamide, Caelix. A patients with recurrent RMS in the upper extremities underwent local

treatment with arterial Cisplatin. 2 patients were treated with high dose CT and autologous transplantation.

Response and outcome

6 patient were not evaluable for response to the two initial T/C cycles: local treatment (RT/surgery) was used at relapse before T/C administration in 4 patients; 2 other patients were not evaluated according established criteria for response to T/C CT. Overall in 32 evaluable patients, 2 CR and 7 PR were documented, for an overall response rate of 28%. A minor response was recorded in 3 cases. 11 were PD, 9 SD. When any type of tumor size reduction (complete, partial, minor) was considered, a 37.5% response rate was calculated (12/32). 5 years OS was nearly 17%, 5 years PFS was 14%.

Alveolar RMS seem to have a better response to the T/C regimen with 6/17 objective responses, then 35% (47% considering also MR: 8/17), rare stabilizations, a great number of progressions (8/17: 47%); favorable RMS showed 3/15 (20%) responses (26% considering MR); but many stable disease (8/15: 53%) and few progressions.

Among 5 evaluable patients relapsed on therapy 5 had no response (neither a minor 1) and usually progressed to T/C. Among 24 evaluable patients who relapsed after completing CT, 9 had a good response to second line CT and 3 had a minor response.

Toxicity

Toxicity of T/C based chemotherapy was mainly haematological: 24 out of 38 patients experienced neutropenia or anemia or thrombocytopenia, some of them with concomitant fever. One patient experienced cytopenia and tubulopathy, one patient experienced cytopenia and mucositis, 1 suffered isolated nephrotoxicity. A heart disease was discovered in a child after receiving the combination. 6 out of 33 had no toxicity. 4 patients had no data about chemotherapy toxicities. Overall 8 patients are currently alive; 30 are dead.

DISCUSSION

The treatment of patients with refractory RMS is still problematic and patients prognosis is still poor. It’s a habit to treat refractory patients with drugs not used during first line treatment in attempt to overcome drug resistance. Campthotecin derivatives are

anticancer agents that inhibit Topoisomerase I activity; among of them are Irinotecan and Topotecan; both have shown promising results in preclinical studies on human tumor xenografts derived from pediatric tumors such as RMS and medulloblastoma (MDB) (2, 3, 4). Phase I clinical trials confirmed the preclinical findings both in adults (5, 6) and children (7, 8, 9). Phase II studies in children confirmed the achieved improvement in neuroblastoma and RMS (10, 11, 12). Carboplatin has known activity against a variety of pediatric solid tumors, either alone or in combination therapy, and is less toxic than Cisplatin (CDDP) and than most other agents. The use of T after a DNA damaging agents such as Carboplatin is appealing in that T may prevent repair of Carboplatin-induced damage (13). For the above reasons, T and C seemed a rational combination for clinical exploration in pediatric malignancies.

As a consequence we designed a T/C based protocol for patients relapsing after been treated in one of the STSC protocols. As a first step we analyzed tumor and patients characteristics to find out factors important in determining the first and second line treatment response rate. Previous studies found that tumor histology, tumor primary site, type of recurrence and temporal relation to therapy were associated significantly with prognosis in patients with recurrent RMS (14). In fact OS of patients who suffers distant relapse differs dramatically from who suffer only local recurrence (15). The timing of recurrence also influence prognosis. OS for patients whose disease recurred on therapy was significantly lower than patients with late failures (14). Similar results were published by IRSG and CWS were the prognosis of relapsed patients was significantly different between patients who developed recurrence after completing CT compared with patients who had developed recurrence while receiving CT (19% vs. 2,7% $P<0,05$) (16). Our data do not permit to calculate time of recurrence but we can say that patients whose disease progressed soon during first line CT or did not show a good response to first courses showed no response even to second line CT and discouraging outcome.

In our study IRS stage seems to affect prognosis (statistical significance for OS, a trend was evident for PFS). Furthermore, primary site seem to be linked to response rate. In fact, 7 out of 8 patients with no response to first line CT were located in an unfavorable primary site (4 of them were PM). We found the same data in non-responders to second line CT: the primary site of the tumor was unfavorable in 18 out of 20 patients who did not show any sensitivity to T/C regimen.

About treatment of relapsed patients, to date few phase II trials have been performed; in most of the studies the total evaluable population was small (often <20 patients) and heterogenous (MDB, osteosarcomas, PNET, RMS…). Our series included only patients with RMS; 32 patients out of 38 were evaluable for response; an overall response rate (ORR) of 28% has been obtained with a 3 years progression free survival (PFS) of 17% and a 3 years overall survival (OS) of 24%. This results seem not so satisfactory; but it has to be taken into account the poor prognosis of these heavily pretreated patients and the limited success obtained with many other drugs in the same setting. Drugs belonging to adult oncology like Oxaliplatin, Gemcitabine, 5 Fluorouracil, Taxanes, showed very limited activity in pediatric solid tumors (17, 18). Interesting comparison could be done with Vinorelbine and Irinotecan. In fact both these molecules, alone as well as administered with other drugs, demonstrated encouraging results; Vinorelbine (VNB) is a vinca alkaloid agent with a well known tolerability profile and activity in pediatric solid tumors; some studies assessed efficacy and tolerability of combination of VNB and Cyclophosphamide (19); this combination yielded a ORR 34-36% and a median survival time of 9 months (20). Irinotecan showed a ORR of 23% in a study with a protracted schedule (21); a ORR of 31,5% and a 3 y PFS of 15% were obtained when combined with VCR (randomized phase II window trial by COG) (22). The combination Irinotecan, VCR and Temozolomide (TMZ) has been tested in a phase I trial (23); a very good antitumor activity was obtained and based on these data the European Soft Tissue Sarcoma Group is evaluating a phase II trial to test a combination of Irinotecan with VCR +/- TMZ. A very good result has been obtained with the combination of Topotecan and Cyclophosphamide: 10/15 RMS showed an objective response (67% ORR) in the phase II by POG (24).

According to the above mentioned data, the ORR obtained with Topotecan/Carboplatin is not so satisfactory but neither much worse than the results highlighted with some other combinations. Especially if we consider minor responses (MR) too we obtain a 37,5% ORR; interestingly also a great number of stabilizations were observed (9/32: 28%). Emerged an interesting difference in response rate between unfavorable RMS and favorable RMS: alveolar RMS seem to have a better response to the T/C regimen versus what observed in favorable RMS: 35% (47% considering MR too) versus 20% (26% with MR). Mascarenhas and Colleagues too found a higher RR by unfavorable RMS compared with favorable RMS, 48% versus <20%.

Toxicity of T/C based chemotherapy was mainly haematological and mild, usually reversible.

At relapse to T/C based CT no "standard" treatment is known to be effective. Than a variety of strategies have been used in our series: RT and surgery if not performed before; metronomic CT (low dose VNB, Cyclophosphamide, Etoposide), high dose CT, Irinotecan, VAC, GEMOX (Gemcitabine+Oxaliplatin) and so on. Because of this heterogeneity it is difficult to interpret data on OS in relation to T/C efficacy.

We conclude that T/C based CT is very well tolerated with similar results in terms of RR. We consider it an option but these results are not so satisfactory. The rarity of the disease complicate the researchers work; an effort has to be done to enroll patients in clinical trials, eventually up to 21 years and join data and expertise. There is a strong need to individualize treatment (e.g. alveolar RMS good responder to T/C versus non alveolar?), to find out new molecular targets, new drugs or new schedules to improved prognosis of these young patients.

FIG 1: Treatment schedule

20.1.1 SECOND LINE TREATMENT SCHEMA

Topo - Carbo Regimen

	Topo Carbo	Topo Carbo	*Good Response*	Topo Cyclo	VP16 Carbo	Topo Cyclo	VP16 Carbo
weeks	1	4		7	10	13	16
			Tumour response evaluation				

Topotecan: 2 mg/m^2/day on day 1 to 3 (total dose 6 mg/m^2/course).
Carboplatin: 250 mg/m^2/day on day 4 and 5 (total dose 500 mg/m^2 course)
Cyclophosphamide: 1500 mg/m^2 /day on day 1 and 2 (total dose 3000 mg/m^2 course)
VP16: 100 mg/m^2/day on day 1 to 3 (total dose 300 mg/m^2 course)

Doxo – Carbo Regimen

	Doxo Carbo	Doxo Carbo	*Good Response*	Doxo Cyclo	Doxo Carbo	Doxo Cyclo	Doxo Carbo
weeks	1	4		7	10	13	16
			Tumour response evaluation				

Doxorubicin: 60 mg/m^2/day on day 1 (total dose 60 mg/m^2/course, 10 mg/m^2/h)
Carboplatin: 250 mg/m^2/day on day 1 and 2 (total dose 500 mg/m^2 course)
Cyclophosphamide: 1500 mg/m^2 /day on day 1 and 2 (total dose 3000 mg/m^2 course)

Chemotherapy modulation

The interval between courses should be 21 days and the following chemotherapy course should not be started unless all these conditions are present:

- 2 x10^9/l WBC, or 1 x10^9/l neutrophils
- 80 x10^9/l platelets are reached.
- absence of any relevant organ dysfunction

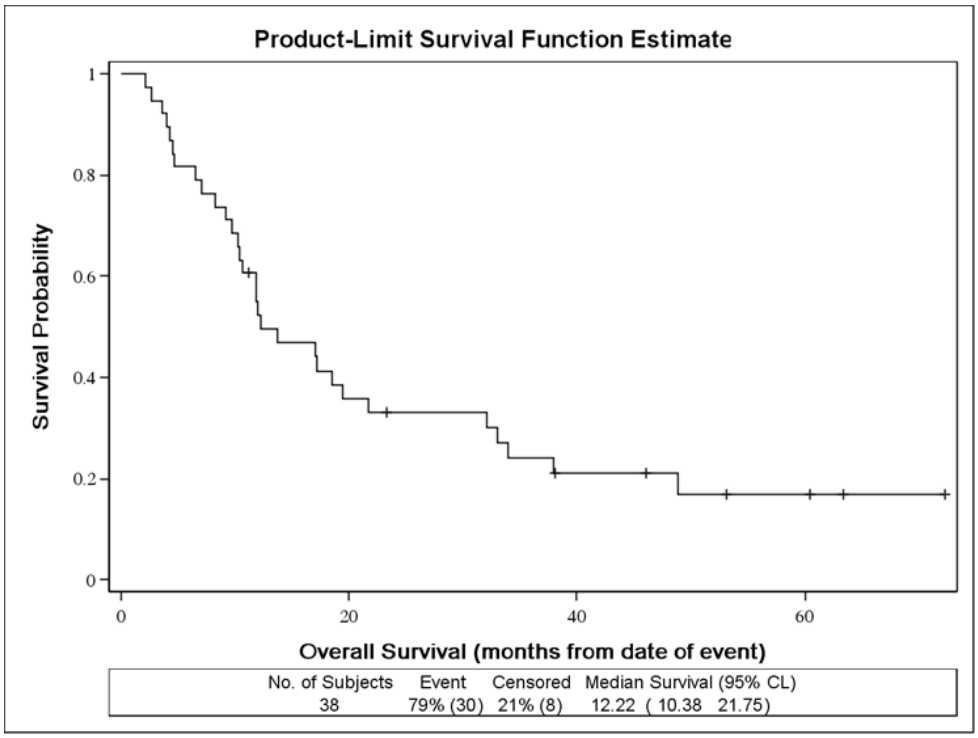
Response assessment

This should be done according to the same recommendations and criteria adopted for the first line treatment (see paragraph 19.1). However the tumour volume after the initial two courses of second line chemotherapy must be compared to the tumour evaluated at week 9th and not at diagnosis.

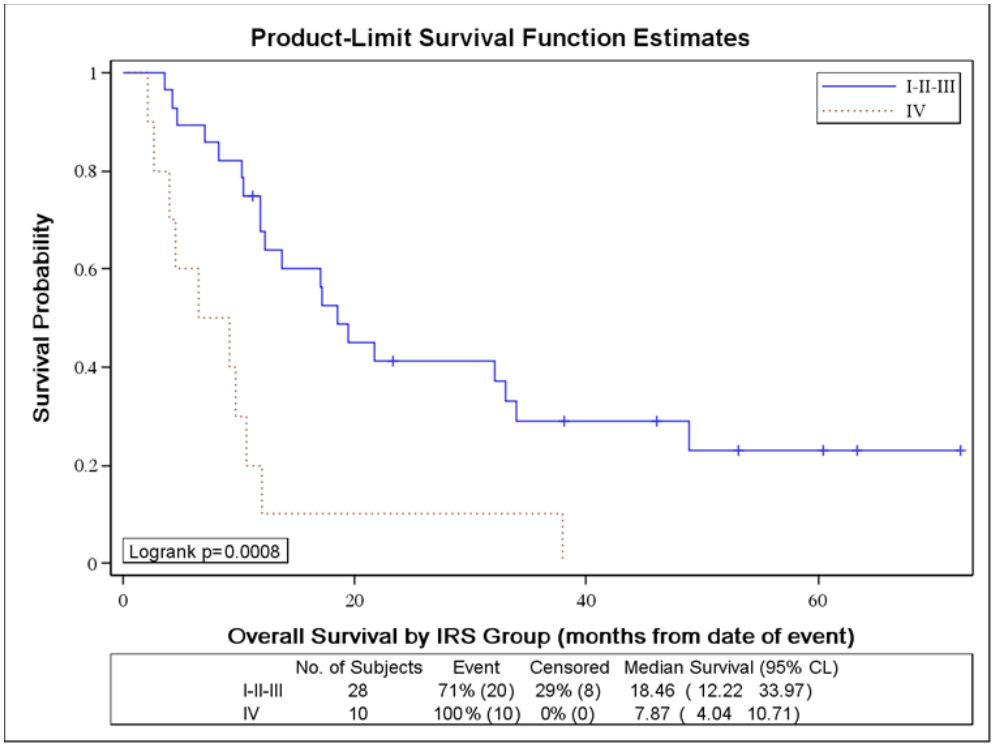
TABLE 2 Tumor characteristics

Sex	
- Male	16
- Female	22
Primary Site	
- Orbit	1
- Head and Neck non Parameningeal	4
- Head and ne ckParameningeal	9
- Genito-Urinary Bladder Prostate	3
- Genito-Urinary non Bladder Prostate	3
- Extremities	9
- Other sites	9
Histology	
Alveolar	18
Embrional	18
Spindle cell	1
Unknown	1
T stage	
T1	15
T2	22
Unknown	1
N stage	
N0	21
N1	16
Nx	1
Tumor size	
$\leq$ 5 cm	12
> 5 cm	25
Unknown	1
IRS group	
I/II/III	28
IV	10

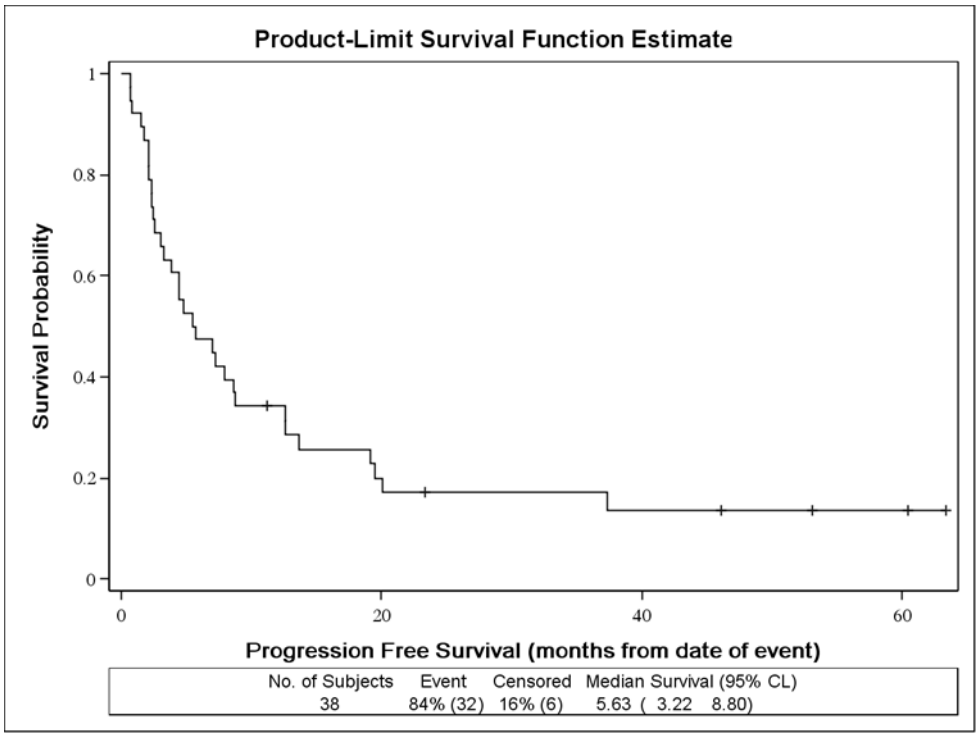
Overall Survival



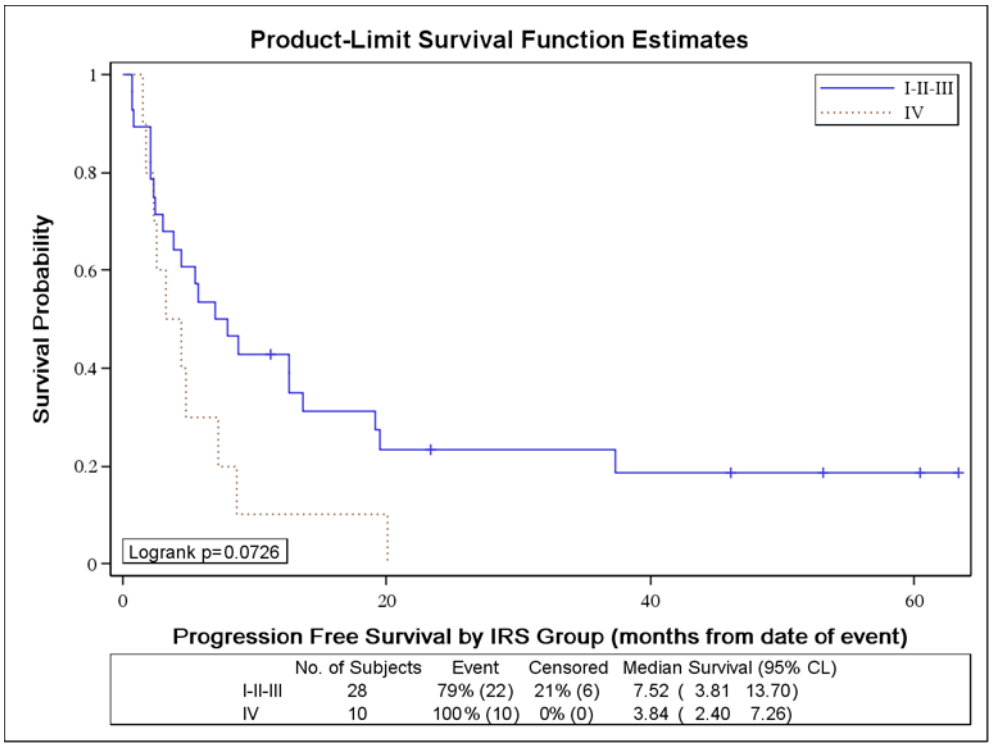
Overall Survival by IRS Group



Progression Free Survival



Progression Free Survival by IRS Group



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3 I NUOVI FARMACI

3.1 Introduzione

Negli ultimi anni il miglioramento delle tecniche di diagnostica, la ricerca in ambito farmacologico e l'approccio multimodale, hanno permesso un aumento della sopravvivenza dei bambini e adolescenti affetti da tumore. Mentre negli anni '50 la quasi totalità dei casi esitava nel decesso, siamo giunti ora ad una sopravvivenza a 5 anni del 75% (1). I maggiori successi sono stati ottenuti nell'ambito delle patologie ematologiche (leucemie e linfomi) mentre i risultati ottenuti nei tumori solidi sono stati meno eclatanti.

La prognosi dei pazienti affetti da tumore dipende molto dallo stadio all'esordio: la sopravvivenza dei pazienti pediatrici affetti da rabdomiosarcoma (RMS) arriva, per esempio, al 70% quando la malattia è localizzata, ma scende al di sotto del 30% per i pazienti con malattia metastatica (2). La prognosi è particolarmente severa anche per i pazienti con malattia in recidiva e/o resistente al trattamento chemioterapico di prima linea. Risulta quindi di fondamentale importanza ricercare nuove strategie terapeutiche per i pazienti con malattia metastatica all'esordio o resistente al trattamento di prima linea. A tale scopo numerose sono le vie percorribili: lo studio di nuovi farmaci, di nuove schedule/combinazioni di farmaci noti, di formulazioni adatte alla somministrazione a pazienti pediatrici.

L'ambito dei nuovi farmaci include sia le molecole/farmaci di ultima generazione che tanto hanno segnato la ricerca più recente (inibitori delle tirosin kinasi, anticorpi monoclonali), sia i farmaci non ancora utilizzati nel paziente pediatrico ma che ormai fanno parte del trattamento standard negli adulti.

La ricerca ha via via identificato lo stretto legame esistente tra genetica e tumore. L'utilizzo di tecniche sempre più sofisticate di analisi ha permesso di studiare alcune delle basi molecolari del processo neoplastico e la ricerca sui farmaci antineoplastici si è recentemente focalizzata sulla cosiddetta "target therapy". Le basi molecolari e le anomalie genetiche implicate nella malattia cancro, determinano uno squilibrio nella produzione/attivazione di alcune molecole. La determinazione della struttura delle molecole coinvolte ha permesso di "costruire" inibitori altamente selettivi in grado di interferire/bloccare i pathways cellulari erroneamente up/down regolati nel processo neoplastico. I successi ottenuti con alcune molecole hanno dato una spinta alla ricerca in

tale ambito: Imatinib, inibitore del recettore della tirosin-chinasi che blocca l'attività dei recettori c-Abl, c-Kit e PDGF, costituisce ad esempio uno dei più eclatanti successi della target therapy: il farmaco è divenuto rapidamente trattamento standard per i pazienti affetti da tumori gastrointestinali stromali e leucemia linfatica cronica. Dati preclinici promettenti riguardano anche molecole quali gli inibitori delle metalloproteinasi e gli inibitori di alcuni fattori di crescita quali VEGF, PDGF, EGF e dei loro recettori (3).

Interferire con i pathways cellulari sregolati nella cellula neoplastica è sicuramente una via da percorrere. La ricerca deve pertanto perseguire tale obiettivo e gli studi clinici di fase I, II e III sulle "nuove molecole" sono uno strumento di fondamentale importanza, ancillare agli studi di laboratorio che ne costituiscono la base. Tuttavia, se l'inibizione di pathways coinvolti può essere una strategia efficace, non va sottostimato il fatto che vi sono molte alterazioni genetiche e più vie coinvolte in un tipo di tumore; molti processi biologici inoltre hanno vie "alternative" che possono potenzialmente bypassare il pathway con il quale il farmaco interferisce. Una spia di ciò è la non completa concordanza di risultati tra sperimentazione preclinica e clinica, soprattutto quando le molecole in studio vengono utilizzate da sole. Inoltre non vanno dimenticati i potenziali effetti collaterali dovuti ai molteplici ruoli che la molecola target può possedere e va considerata la possibilità dell'insorgenza di resistenze. Questo dimostra come probabilmente sia necessario pensare a dei "pannelli" di farmaci che mirino a bloccare i numerosi pathways coinvolti nel processo neoplastico. Tali premesse suggeriscono inoltre che la target therapy è una delle vie, ma non può essere la sola arma contro una patologia tanto complessa.

E' quindi importante non tralasciare le altre vie possibili: in particolare considerare schedule che prevedano la somministrazione di farmaci a bassi dosaggi ma in modo continuativo ("terapia metronomica"): risultati di studi recenti suggeriscono che la somministrazione di alcuni farmaci citotossici a basse dosi aumenta l' effetto antiangiogenico dei farmaci. Tale approccio potrebbe essere utile per minimizzare la tossicità dei farmaci, soprattutto in pazienti che necessitano di trattamenti molto prolungati. I farmaci citotossici possono essere in quest'ottica associati alle nuove molecole, quali gli inibitori del VEGFR, per un reciproco potenziamento (4).

Anche l'utilizzo di chemioterapici mutuati dall'esperienza nell'adulto dei quali esistano dati di efficacia su linee cellulari di tumori solidi pediatrici (es.: inibitori delle Topoisomerasi, Taxani…) è una via percorribile (5, 6).

Altra possibilità che si prospetta è lo studio della farmacologia di farmaci in uso in Oncologia Pediatrica (quali ad esempio le antracicline) volti ad ottimizzarne l'utilizzo (7).

Da tali premesse emerge la complessità del problema e la molteplicità delle vie che vanno percorse.

Le prospettive delineate rientrano nell'ottica di una visione "allargata" del problema: come sottolineato recentemente (8), la ricerca di nuovi agenti antitumorali è fondamentale e deve applicarsi su più fronti possibile, ma senza focalizzarsi su un'unica strategia. Le molecole di nuova generazione (target therapy) sono promettenti ma probabilmente non costituiranno, sole, la soluzione ad un problema tanto complesso. E' necessario trovare le vie più adeguate per il miglior utilizzo dei farmaci nuovi e vecchi.

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3.2 Trials clinici

Il RMS è una neoplasia altamente chemiosensibile con ottimi tassi di risposta alla terapia di prima linea. Tuttavia i tassi di risposta e la prognosi di pazienti refrattari alla terapia di prima linea o che ricadono al termine della terapia di prima linea sono deludenti.

La ricerca sui nuovi farmaci nell'ambito dell'Oncologia Pediatrica ha subito una notevole spinta negli ultimi anni proprio sulla base della necessità di migliorare la prognosi di questi pazienti. Le Aziende Farmaceutiche hanno manifestato un interesse crescente e chi lavora con la patologia neoplastica pediatrica sta iniziando a conoscere la complessità dell'iter che porta un farmaco dal laboratorio alla clinica passando per gli studi clinici di fase I, II, III.

Gli studi clinici rendono possibile la raccolta di dati su tossicità, minima dose efficace, efficacia del farmaco testato da solo e in combinazione. Costituiscono il punto di passaggio obbligato e strettamente "controllato" per l'approvazione di un farmaco; per i pazienti la partecipazione a tali trials rappresenta una chance terapeutica; infatti si tratta di pazienti con patologia non più responsiva alla terapia standard, con poche prospettive terapeutiche (o nulle) e cattiva prognosi; hanno accesso attraverso i protocolli a "nuovi" farmaci potenzialmente efficaci (o più efficaci di altri) prima che questi siano sul mercato e godono di una supervisione specialistica particolarmente attenta e stretta; a tale proposito ricordo i dati già esposti in precedenza (capitolo 1) relativamente ai pazienti adolescenti/giovani adulti il cui scarso tasso di arruolamento nei trials clinici correla con la loro peggior prognosi (capitolo 1).

Il Centro che partecipa al trial offre una chance terapeutica in più al paziente, può di conseguenza costituire "polo attrattivo"/di riferimento per altri centri minori a fallimento della terapia standard; per il Centro partecipare ad un trial clinico comporta la disponibilità di risorse e una adeguata expertise da parte del personale dedicato; a questo scopo da alcuni anni il nostro gruppo ha iniziato un percorso formativo nell'ambito dei trials clinici per figura medica, infermieristica e amministrativa (data manager). In tal modo è aumentata l'expertise necessaria e il Centro ha via via avviato la partecipazione a un numero sempre maggiore di protocolli di fase II e III nazionali e internazionali focalizzati prevalentemente su pazienti affetti da tumori solidi pediatrici refrattari/recidivi. Questo ha permesso al nostro Centro di diventare attualmente uno dei Centri Italiani con maggior offerta di trials clinici.

Partecipare alla ricerca su nuovi farmaci significa collaborare con numerosi partners in ricerca medica clinica, ricerca di base, aziende del settore del farmaco; per quanto concerne i tumori solidi pediatrici (in particolare i sarcomi delle parti molli), tra questi vi sono l'EpSSG (European Pediatric Soft Tissue Sarcoma Group), l' ITCC (Innovative Therapies for Children with Cancer), Conticanet (CONNective TIssue CAncer NETwork), l'EMEA (European MEdicines Agency), ENCCA (European Network for Cancer Research in Children and Adolescents); l'obiettivo comune di tale collaborazione è trovare terapie innovative per la cura di pazienti pediatrici e adolescenti con sarcoma e uniformare le strategie dei centri europei per garantire standard di cura ottimali ai pazienti.

Segue l'elenco dei trials a cui il Gruppo/Centro ha partecipato negli ultimi anni e sta partecipando, con lo stato dell'arte.

Indication of Trial	**Clinical Phase of Trial (I-IV)**	**Year in which trial was conducted**
Open-Label trial of Glivec (imatinib mesylate) in patients with refractory desmoplastic small round cell tumors (DSRCT) expressing a molecular target of Glivec (PDGF-R and/or C-kit)	II	Close 2010
GEMOX: Studio di fase 2 con gemcitabina in combinazione con oxaliplatino nei tumori solidi pediatrici refrattari recidivati.	II	Close 2009
BERNIE: Open-label, multi-center, randomized, two stage adaptive design study of the combination of bevacizumab with standard chemotherapy in minor patients with metastatic high risk rhabdomyosarcoma, non-rhabdomyosarcoma soft-tissue sarcoma or high risk Ewing's sarcoma/soft-tissue PNET	II	2009- still open
TOTEM 2: Phase 2-single arm studies of Temozolomide in combination with Topotecan refractory and relapsed neuroblastoma and other pediatric solid tumours	II	2009- still open
"Studio di fase III sull'efficacia dell'intensificazione della dose in pazienti con sarcoma di Ewing non metastatico (**ISG/AIEOP EW1**)"	II	2010-still open
Protocollo terapeutico con chemioterapia ad alte dosi, radioterapia, terapia di mantenimento con ciclofosfamide a basse dosi e anti-COX 2 per sarcoma di Ewing metastatico: studio ISG/AIEOP (**ISG/AIEOP EW-2**)"	II	2009-still open
A Study to Determine the Activity of SCH 717454 in Subjects With Osteosarcoma or	II	Close July 2010

Ewing's Sarcoma That Has Relapsed After Standard Systemic Therapy (**Protocol No. P04720**)		
Phase II, open label, non-randomized study of second or third line treatment with sorafenib (**BAY 43-9006**) in patients affected by relapsed high-grade osteosarcoma.	II	2009- still open
A Phase 1/2 Combined Dose Ranging and Randomised, Open-label, Comparative Study of the Efficacy and Safety of Plerixafor (**Mozaic**) in Addition to Standard Regimens for Mobilisation of Haematopoietic Stem Cells into Peripheral Blood, and Subsequent Collection by Apheresis, Versus Standard Mobilisation Regimens Alone in Paediatric Patients, Aged 2 to <18 Years, with Solid Tumours Eligible for Autologous Transplants	II	2010- still open
Epoc-Doxo: Phase II pharmacokinetic study to assess the age dependency in the clearance of doxorubicin in paediatric patients with solid tumours and leukaemia	II	2010- still open
APREPITANT: MK0869-208 "A Phase III, Randomized, Double-Blind, Active Comparator-Controlled Clinical Trial, Conducted Under In-House Blinding Conditions, to Examine the Efficacy and Safety of Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) in Pediatric Patients"	III	2011- still open
HERBY: A phase II open-label, randomized, multi-centre comparative study of bevacizumab-based therapy in paediatric patients with newly diagnosed supratentorial high-grade glioma.	II	2011- still open

PETIT2: A phase III, two part, double-blind, randomized, placebo-controlled and open-label study to investigate the efficacy, safety and tolerability of eltrombopag, a thrombopoietin receptor agonist, in pediatric patients with previously treted chronic immune (idiopathic) thrombocytopenic purpura (ITP).	III	2012
VIT: International randomized phase II study of the combination of vincristine, and irinotecan with or without temozolomide in patients with refractory o relapsed rhabdomyosarcoma.	II	2012- still open
GIST: A Phase I/II study of Sunitinib in young patients with advanced gastrointestinal stromal tumor.	I/II	2012 - still open
MEPACT: Phase IV Surveillance study of patients with newly diagnosed high-grade, resectable non metastatic osteosarcoma to investigate the short-term safety profile of mifamurtide (MEPACT) as part of a combined chemotherapy treatment regime for this condition.	IV	2012 - still open

3.3 Protocollo di fase II

3.3.1 Introduzione

Parte integrante del progetto era il raggiungimento di una adeguata expertise per la stesura di Protocolli di fase II-III. Tale obiettivo è stato raggiunto grazie alla formazione in itinere attraverso partecipazione a corsi specifici come:

- "*ITCC Training Days*", corso sullo sviluppo di nuovi farmaci in oncologia pediatrica, tenutosi a Roma dal 22 al 24 ottobre 2009.
- "*3rd ESO-SIOP Europe Masterclass in paediatric oncology*", tenutosi a Castelgandolfo, Roma, dal 12 al 18/06/2010.

Inoltre la partecipazione attiva e via via crescente come subinvestigator a trials clinici di fase II e III, nazionali e internazionali, ha contribuito ad una progressiva conoscenza del percorso che porta alla stesura dei protocolli e della loro gestione; la formazione di un Gruppo dedicato ai "Nuovi Farmaci" è uno dei risultati di questo lavoro e costituisce senza dubbio un valore aggiunto per il Nostro Centro.

Il gruppo è formato da:

Data Managers per la raccolta dati, la compilazione delle CRF (case reporting form) con supervisione medica, le relazioni con i centri coordinatori, i Monitors, le aziende sponsor, i comitati etici.

Infermiere di Ricerca dedicate a seguire i pazienti arruolati nei protocolli (contabilità e conservazione del farmaco, preparazione e somministrazione della chemioterapia, relazione col paziente e i famigliari negli aspetti di loro competenza, feedback a medici e data managers).

Medici dedicati alla gestione superspecialistica dei pazienti in protocollo, con valutazione dell'eligibilità dei pazienti al protocollo, arruolamento degli stessi, consegna, spiegazione, firma dei consensi, prescrizione della chemioterapia, controllo e gestione degli eventi avversi (in particolare i "SAE", serious adverse events), supervisione delle CRF.

Il coinvolgimento come subinvestigator con la fondamentale partecipazione a Investigators' Meeting (es: Windsor il 22-23.05.2008 per il Protocollo BO20924, Heathrow il 24.03.2009 per il Protocollo BO20924, Madrid il 19-20.01.2010 per il Protocollo BO20924) ed a visite di apertura del Centro ai protocolli, ha permesso

l’acquisizione di una certa expertise in questo ambito, frontiera relativamente “nuova” per il mondo pediatrico.
A “conclusione” di tale iter formativo gli sforzi sono stati coordinati alla stesura di un protocollo di fase II per le recidive di tumori solidi pediatrici.
L’oggetto del protocollo è il trattamento delle meningosi da RMS/EPNET con topotecan intratecale. La stesura del protocollo è in corso, la versione definitiva verrà probabilmente presentata alla riunione annuale sui tumori solidi pediatrici che si tiene a Padova verso la fine dell’anno.

Segue quanto finora scritto del protocollo di fase II.

3.3.2 Phase II study of intrathecal topotecan in leptomeningeal relapsed rhabdomyosarcoma and Ewing PNET children and adolescents.

SYNOPSIS

Title:	Phase II study of intrathecal topotecan in leptomeningeal relapsed rhabdomyosarcoma and Ewing PNET children and adolescents.
Principal Investigator	Dr Gianni Bisogno
Study centers	Hemato-oncology Department of Padua (coordinating centre) AIEOP centres/European hemato-oncology Hospitals
Objectives	*Primary*: determine the therapeutic activity of IT Topotecan in terms of Response rate and time to CNS progression in pediatric patients with RMS/EPNET tumors and leptomeningeal dissemination. *Secondary*: assess duration of response, overall survival, safety and toxicity
Study design	Prospective non randomized phase II trial
Number of patients	RMS: EPNET:
Inclusion criteria	Histologically confirmed RMS or Ewing PNET sarcoma with leptomeningeal involvement (see assessment of CNS dissemination). CNS dissemination: positive CSF citology examination or unequivocal evidence of leptomeningeal disease on CT scan or MRI scan. Patients < 21 years of age. Patients, parents or legal representatives must provide written informed consent. Life expectancy of at least 8 weeks. KPS > 60%. Adequate organ function:

Adequate *haematological* function: haemoglobin ³ 80 g/l, neutrophil count ³ 1.0 x 109/L, platelet count ³ 100 x 109/L; in case of bone marrow disease: neutrophils ³ 0.5 x 109/l and platelets 75 x 109/l;

Adequate *renal* function: normal creatinine related to patient's age:

- o 0 – 1 year: 40 μmol/L
- o 1 – 15 years: 65 μmol/L
- o 15 – 20 years: 110 μmol/L

Adequate *hepatic* function: bilirubin 1.5 x ULN; AST and ALT 2.5 x ULN (AST, ALT 5xULN in case of liver metastases)

Wash-out of 3-4 weeks in case of prior chemotherapy.

Concurrent CT to control systemic disease is allowed if the systemic CT is not a phase I agent that significantly penetrates the CSF or an agent known to have serious unpredictable CNS side effects.

Concurrent dexamethasone or prednisone allowed if part of a systemic CT regimen.

At least 8 weeks since prior cranial irradiation and recovered.

At least 14 days since prior investigational drug.

Fertile patients must use effective contraception.

Patient/family able to comply to the study protocol.

Exclusion criteria

Clinical evidence of obstructive hydrocephalus.

Serious concomitant systemic disorders.

History of allergic reaction to study drug.

Pregnant or breast feeding mothers.

Concurrent whole brain or craniospinal irradiation.

Treatments

Induction: Topotecan IT 0,4 mg/dose twice weekly for 6 weeks

Consolidation: Topotecan IT 0,4 mg/dose weekly for 4 weeks

	Maintenance: Topotecan IT 0,4 mg/dose twice monthly for 4 months then monthly through year 1
Assessment and	
Criteria for evaluation	*Efficacy:* MRI/CT scans CSF cytology (LP/intraventricular reservoir) *Safety:* Safety profile will be evaluated. Clinical and laboratory toxicities/symptomatology will be graded according to NCI-Common toxicity criteria AE v3.0. The adverse events which are not reported in the NCI-Common toxicity criteria will be graded as mild, moderate, severe, life-threatening
Statistical method	
Post study follow up	Every 2 months up to death or study cut-off.

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BACKGROUND

Rhabdomyosarcoma/PNET

Incidence and Epidemiology

Childhood rhabdomyosarcoma, a soft tissue malignant tumor of mesenchymal origin, accounts for approximately 3.5% of the cases of cancer among children aged 0 to 14 years and 2% of the cases among adolescents and young adults aged 15 to 19 years (2, 3). The incidence is 4.5 per 1 million children and 50% of cases are seen in the first decade of life (4). Most cases of rhabdomyosarcoma occur sporadically, with no recognized predisposing factor or risk factor (8). Genetic conditions associated with rhabdomyosarcoma include Li-Fraumeni cancer susceptibility syndrome (with germline p53 mutations), (9, 10, 11) pleuropulmonary blastoma (with DICER1 mutations), (12, 13) neurofibromatosis type I, (14) Costello syndrome (with germline HRAS mutations), (15-18) Beckwith-Wiedemann syndrome (with which Wilms tumor and hepatoblastoma are more commonly associated), (19, 20) and Noonan syndrome. (18, 21, 22)

Dramatic improvements in survival have been achieved for children and adolescents with cancer (1). Between 1975 and 2002, childhood cancer mortality has decreased by more than 50%. For rhabdomyosarcoma, the 5-year survival rate has increased over the same time from 53% to 65% for children younger than 15 years and from 30% to 47% for adolescents aged 15 to 19 years (1).

RMS may arise everywhere in the body. The most common primary sites for rhabdomyosarcoma are the head, the genitourinary tract, and the extremities (5, 6). Within extremity tumors, tumors of the hand and foot occur more often in older patients and have an alveolar histology; these tumors also have a higher rate of metastatic spread (7). Other less common primary sites include the trunk, chest wall, perineal/anal region, and abdomen including the retroperitoneum and biliary tract. Symptoms depend on the site of origin.

Prognostic Factors

The prognosis for a child or adolescent with rhabdomyosarcoma is related to the age of the patient, site of origin, tumor size (widest diameter), resectability, presence of metastases, number of metastatic sites or tissues involved, presence or absence of

regional lymph node involvement, histopathologic subtype (alveolar vs. embryonal), and delivery of radiation therapy in selected cases (5, 6, 23-30) as well as unique biological characteristics of rhabdomyosarcoma tumor cells (31). It is unclear whether response to induction chemotherapy, as judged by anatomic imaging, correlates with the likelihood of survival in patients with rhabdomyosarcoma, as one study found an association and another study did not (32, 33).

Rhabdomyosarcoma is usually curable in most children with localized disease who receive combined-modality therapy, with more than 70% surviving 5 years after diagnosis (5, 6, 34). Local relapses are more frequent than metastatic ones. Relapses are uncommon after 5 years of disease-free survival, with a 9% late-event rate at 10 years. Relapses, however, are more common for patients who have gross residual disease in unfavorable sites following initial surgery and those who have metastatic disease at diagnosis (35).

Cellular and molecular classification

Rhabdomyosarcoma can be divided into several histologic subsets: embryonal rhabdomyosarcoma, which has embryonal, botryoid, and spindle cell subtypes; alveolar rhabdomyosarcoma; and pleomorphic rhabdomyosarcoma (36,37).

Embryonal Rhabdomyosarcoma: the embryonal subtype is the most frequently observed subtype in children, accounting for approximately 60% to 70% of rhabdomyosarcomas of childhood (36).Tumors with embryonal histology typically arise in the head and neck region or in the genitourinary tract, although they may occur at any primary site. Embryonal tumors often show loss of specific genomic material from the short arm of chromosome 11 (44,45, 46). The consistent loss of genomic material at the chromosome 11p15 region in embryonal tumors suggests the presence of a tumor suppressor gene, although no such gene has yet been identified.

Botryoid and spindle cell subtypes: botryoid tumors represent about 10% of all rhabdomyosarcoma cases and are embryonal tumors that arise under the mucosal surface of body orifices such as the vagina, bladder, nasopharynx, and biliary tract.

The spindle cell variant of embryonal rhabdomyosarcoma is most frequently observed at the paratesticular site (38). Both the botryoid and the spindle cell subtypes are associated with very favorable outcomes (37).

Alveolar Rhabdomyosarcoma: approximately 20% of children with rhabdomyosarcoma have the alveolar subtype. An increased frequency of this subtype is noted in adolescents and in patients with primary sites involving the extremities, trunk, and perineum/perianal region (36).

Unique translocations between the FOXO1 (previously called FKHR) gene on chromosome 13 and either the PAX3 gene on chromosome 2 (t(2;13)(q35;q14)) or the PAX7 gene on chromosome 1 (t(1;13)(p36;q14)) are found in 70% to 80% of patients with alveolar histology tumors (42, 43, 44). Translocations involving the PAX3 gene occur in approximately 59% of alveolar rhabdomyosarcoma cases, while the PAX7 gene appears to be involved in about 19% of cases (42).

Pleomorphic (Anaplastic) Rhabdomyosarcoma: pleomorphic rhabdomyosarcoma occurs predominantly in adults aged 30 to 50 years and is rarely seen in children (39). In adults, pleomorphic rhabdomyosarcoma is associated with a worse prognosis. In children, the term anaplasia is preferred (40). In a retrospective review of 546 pediatric patients, the presence of anaplasia was only associated in univariate analysis with inferior clinical outcome in patients with intermediate-risk rhabdomyosarcoma (41).

Stage Information

Before a biopsy of a suspected tumor mass is performed, imaging studies of the mass and baseline laboratory studies should be obtained. After the diagnosis of rhabdomyosarcoma has been made, an extensive evaluation to determine the extent of the disease should be done prior to instituting therapy. This evaluation should include a chest x-ray, computed tomography (CT) scan of the chest, bilateral bone marrow aspirates and biopsies, bone scan, magnetic resonance imaging (MRI) of the base of the skull and brain (for parameningeal primary tumors only), and CT scan of the abdomen and pelvis (for lower extremity or genitourinary primary tumors).

A CT or MRI scan of regional lymph nodes should be considered. Abnormal-appearing lymph nodes should be biopsied when possible. One study has demonstrated that sentinel lymph node biopsies can be safely performed in children with rhabdomyosarcoma, and tumor-positive biopsies may alter the treatment plan (47). Positron emission tomography (PET) with fluorine-18-fluorodeoxyglucose (FDG) scans can identify areas of possible metastatic disease not seen by other imaging modalities (48-50). However, the efficacy of these two procedures for identifying involved lymph

nodes or other sites is currently under investigation, and these procedures are not required by current treatment protocols.

As noted previously, prognosis for children with rhabdomyosarcoma depends predominantly on the primary site, tumor size, Group, and histologic subtype. Favorable prognostic groups were identified in previous Intergroup Rhabdomyosarcoma Study Group (IRSG) studies, and treatment plans were designed on the basis of assignment of patients to different treatment groups according to prognosis. Several years ago, the IRSG merged with the National Wilms Tumor Study Group and two large cooperative pediatric cancer treatment groups to form the Children's Oncology Group (COG). New protocols for children with soft tissue sarcoma are developed by the Soft Tissue Sarcoma Committee of the COG (COG-STS). Current COG-STS protocols for rhabdomyosarcoma use the TNM-based pretreatment staging system that incorporates the primary tumor site, presence or absence of tumor invasion of surrounding tissues, tumor size, regional lymph node status, and the presence or absence of metastases (51, 52). After patients are categorized by Stage and Surgical-pathologic Group, a Risk Group is assigned. This takes into account Stage, Group, and histology. Patients are classified for protocol purposes as having a low risk, intermediate risk, or high risk of disease recurrence (53, 54). Treatment assignment is based on Risk Group.

Treatment Option Overview

All children with rhabdomyosarcoma should receive chemotherapy. The intensity and duration of the chemotherapy are dependent on the Risk Group assignment. All children with rhabdomyosarcoma require multimodality therapy with systemic chemotherapy, in conjunction with either surgery, radiation therapy (RT), or both modalities to maximize local tumor control (55-57).

Surgical resection may be performed prior to chemotherapy if it will not result in disfigurement, substantial functional compromise, or organ dysfunction. In most cases, this is not possible, and therefore, only an initial biopsy is performed. The majority of patients have Group III (gross residual) disease.

After initial chemotherapy, Group III patients receive definitive RT for control of the primary tumor. Some patients with initially unresected tumors may undergo second-look surgery (delayed primary excision) to remove residual tumor. This is most appropriate if the delayed excision is deemed feasible with acceptable

functional/cosmetic outcome, and if a modest reduction in radiation dose is expected to significantly reduce the risk of long-term adverse effects. RT is given to clinically suspicious lymph nodes (detected by palpation or imaging) unless the suspicious lymph nodes are biopsied and shown to be free of rhabdomyosarcoma.

The treatment of rhabdomyosarcoma by the Children's Oncology Group (COG) and in Europe (as exemplified by trials from the Intergroup Rhabdomyosarcoma Study Group [IRSG], the Soft Tissue Sarcoma Committee of the COG [COG-STS], and the International Society of Pediatric Oncology Malignant Mesenchymal Tumor [MMT] Group) differs in management and overall treatment philosophy (56). Children are treated with a more or less intense CT according to risk group. Main drugs are Ifosfamide, Actinomicine, Vincristine and Doxorubicine.

Leptomeningeal dissemination of cancer

Neoplastic meningitis results from the spread of malignant cells to leptomeninges and subarachnoid space and their dissemination within the cerebrospinal fluid (CSF) compartment. Malignant cells may reach the subarachnoid space through the blood (arterial or venous), by growing along nerve and vascular sheeths, by migration from a tumor adjacent to CSF or by iatrogenic spread of tumor cells following resection of metastasis (58, 59).

Neoplastic meningitis is a devasting complication of both solid and hematologic tumors and is estimated to occur in 5-8% of cancer patients. Among adults the most common cancers that metastasize to the leptomeninges are breast cancer, lung cancer, melanoma, lymphomas and leukemias; in the pediatric population leukemia is the most common cancer with predilection for leptomeningeal dissemination; however primary central nervous system tumors (medulloblastoma and glioma), other cancers like neuroblastoma, rhabdomyosarcoma and retinoblastoma may also disseminate to the leptomeninges (60).

Despite treatment the median survival duration for patients with neoplastic meningitis is in the range of 8-16 weeks. The impact of neoplastic meningitis is likely to increase in the future as advances in systemic treatment have improved survival but leave the leptomeninges and CSF a sanctuary site (61). The meninges are a sanctuary site because protected by the blood brain barrier (BBB) from the cytotoxic effects of systemic

anticancer therapy. The BBB often prevents efficient penetration of many drugs into the CSF space so that only few systemic chemotherapy agents can produce clinically relevant CSF concentrations and only at high doses; this could produce significant systemic toxicity. Regional delivery of drugs directly into the CSF is pharmacologically advantageous, with small doses producing high CSF concentration with minimal systemic exposure (62). Unfortunately only a limited number of drugs have been found to be safe and efficacious when administered by the intrathecal (IT) route.
Therapeutic approaches for leptomeningeal dissemination of cancer are:
- Radiotherapy (RT)
- Systemic CT
- I.T. CT

Focal RT is performed in the treatment of bulky disease and in patients with CSF flow blocks. In addition focal RT should also be administered to symptomatic areas with a short palliative schedule. Another use of RT is in the treatment of cauda equina syndrome and cranial neuropathies from neoplastic meningitis, whereas craniospinal irradiation is rarely used because of significant systemic toxicity (63).

Systemic CT efficacy is not affected by CSF flow obstruction if compared to IT CT. However systemic CT can be limited by systemic toxicity because it's necessary to administer high doses to reach a clinically relevant CSF concentrations; another difficulty is using an effective treatment for neoplastic meningitis as well as for the underlying disease causing the meningeal spread. High doses methotrexate (MTX) have favorable CSF penetration but considerable systemic toxicity too; moreover MTX is not typically part of standard regimens used to treat many of the underlying tumors, making its incorporation into systemic treatment difficult. Ifosfamide and topotecan are both active but toxic, like MTX. Oral temozolomide and capecitabine have shown interesting results against leptomeningeal dissemination from breast and lung cancer (63).

Intrathecal chemotherapy

CT administration can be undertaken either I.T. via a lumbar puncture (LP) or via an intraventricular device with a catheter into the lateral ventricle by Ommaya reservoir.

IT CT has been used in the treatment of leptomeningeal dissemination even though the extent of its benefit has not been proven in randomized controlled trials and some studies showed discordant evidence. IT treatment offers local therapy with minimum systemic toxicity, and avoiding the BBB drugs are distributed throughout the entire subarachnoid space; although high drug concentrations could be achieved in the CSF, IT CT is not effective for bulky disease in the meninges because intra-CSF agents penetrate only 2-3 mm into such lesions (63).

IT administration of anticancer drugs has been an effective strategy for the primary treatment and prevention of leptomeningeal leukemias and lymphomas, but it has not been effective in patients with neoplastic meningitis from solid tumors or in patients with refractory leptomeningeal leukemias (this results in part from the limited number of agents available for IT administration) (64).

Only a small number of anticancer agents are regularly used: methotrexate, cytarabine, liposomal cytarabine, thiotepa. None of these have resulted in significantly prolonged survival and combination of intra-CSF drugs have not improved outcomes over single agents (61). MTX and liposomal cytarabine are the IT drugs most commonly used for leptomeningeal dissemination in solid tumors. However in the few randomized trials the data were discordant when comparing treatments (65). No one have a significant impact on survival, in the studies available "time to neurological progression" is the most frequently used parameter to evaluate response to treatment; the most common adverse event during IT CT is arachnoiditis/chemical meningitis (66, 67).

Then neoplastic meningitis is still a relevant clinical problem, therefore it is essential to develop new IT agents with novel mechanism of action. In the last few years various experimental IT drugs have been reported upon from small clinical trials, a few case reports, and preclinical studies.

Among them Topotecan showed interesting results.

Intrathecal Topotecan

Topotecan is a topoisomerase I poison that has anticancer activity against a variety of adult and childhood solid tumors. Preclinical studies demonstrated a good CSF penetration capability; 0,1 mg intraventricular dose (equivalent to 1 mg in humans) was defined as a well tolerated dose (68, 69).

The results of these preclinical studies served as the basis for phase I studies of IT topotecan in patients with neoplastic meningitis. The phase I study conducted by Blaney and colleagues (64) proved the feasibility of administering topotecan at 0,4 mg as maximum tolerated dose (MTD) to children and adults with neoplastic meningitis (17 assessable patients, heterogenous histotypes); arachnoiditis was the dose limiting toxicity (DLT). A second phase I study (60) aimed to re-evaluate the dosing schedule for IT topotecan administration based upon preclinical evidence that the antitumor activity of topoisomerase I inhibitors is schedule dependent (70, 69). 19 patients <22 years with leukemias and central nervous system cancer were enrolled. The study demonstrated that intensified dosing of topotecan is feasible (with chemical arachnoiditis being the DLT) but whether shorter or longer duration of exposure to the drug would be superior or not is unknown. Because of many different tumor types enrolled, this study, as well as the first one, cannot make definitive conclusions regarding antitumor activity.

A phase II study by Groves and colleagues (61) analyzed the results obtained with IT topotecan classic schedule administration in 62 adult patients with leptomeningeal dissemination from solid tumors. 40 patients were evaluable; treatment was well tolerated (arachnoiditis being the most common adverse event) but outcomes were no better than those reported in trials that employed other IV CT. Better results have been obtained by IT topotecan administered to 20 children with leptomeningeal leukemia (71): among 16 evaluable patients a 37,5% CR have been achieved with a confirmed mild toxicity. A phase II trial of IT topotecan was performed in children with dissemination to the meninges by medulloblastoma and other solid tumors (72); the treatment was well tolerated, there were no objective responses; however the authors observed a benefit in terms of disease stabilization greater than 5 months in 4 children.

Data available show that:

- leptomeningeal dissemination of tumors is a devasting problem because outcome is very bad and treatments available are very few;
- data about IT topotecan come out studies with heterogeneous and small population of patients;
- results in terms of RR/PFS/OS are disappointing but clinical benefit and stabilizations have been observed;

- at our knowledge no phase II studies have been performed with IT topotecan in patients with rhabdomyosarcoma-EPNET tumors and leptomeningeal spread.
  For this reason with designed a phase II study with IT topotecan in patients with rhabdomyosarcoma-EPNET tumors and leptomeningeal spread.

RMS/EPNET with leptomeningeal dissemination enrolled in STSC protocols

We have found 13 patients with leptomeningeal dissemination from RMS or Ewing PNET tumors enrolled in STSC clinical trials from 1979 to 2013.
Analysis about clinical characteristics and outcome are on going.

OBJECTIVES AND ENDPOINTS

The primary objective is to determine the therapeutic activity of IT Topotecan in terms of Response rate and time to CNS progression in pediatric patients with RMS/EPNET tumors.
The secondary endpoint is to assess duration of response, overall survival, safety and toxicity.

OVERALL STUDY PLAN

STUDY DESIGN
Multicenter, prospective, non randomized phase II trial.

STUDY CENTERS
Italy: Padova, INT Milano, Genova, Roma, Napoli, Bergamo, Torino...
Europe: …

EXPECTED NUMBER OF PATIENTS

PATIENT REGISTRATION

STUDY PERIOD

SUBJECT POPULATION AND SELECTION

INCLUSION CRITERIA

- Histologically confirmed RMS or Ewing PNET sarcoma with leptomeningeal involvement (see assessment of CNS dissemination)
- CNS dissemination: positive CSF citology examination or unequivocal evidence of leptomeningeal disease on CT scan or MRI scan.
- Patients ≤ 21 years of age
- Patients, parents or legal representatives must provide written informed consent
- Life expectancy of at least 8 weeks
- KPS > 60%
- Adequate organ function:

  Adequate haematological function: haemoglobin ³ 80 g/l, neutrophil count ³ 1.0 x 109/L, platelet count ³ 100 x 109/L; in case of bone marrow disease: neutrophils ³ 0.5 x 109/l and platelets 75 x 109/l.

  Adequate renal function: normal creatinine related to patient's age:

  - 0 – 1 year: 40 μmol/L
  - 1 – 15 years: 65 μmol/L
  - 15 – 20 years: 110 μmol/L

  Adequate hepatic function: bilirubin <1.5 x ULN; AST and ALT <2.5 x ULN (AST, ALT 5xULN in case of liver metastases)
- Wash-out of 3-4 weeks in case of prior chemotherapy
- Concurrent CT to control systemic disease is allowed if the systemic CT is not a phase I agent that significantly penetrates the CSF or an agent known to have serious unpredictable CNS side effects
- Concurrent dexamethasone or prednisone allowed if part of a systemic CT regimen
- At least 8 weeks since prior cranial irradiation and recovered
- At least 14 days since prior investigational drug
- Fertile patients must use effective contraception

- Patient/family able to comply to the study protocol

EXCLUSION CRITERIA

- Clinical evidence of obstructive hydrocephalus
- Serious concomitant systemic disorders
- History of allergic reaction to study drug
- Pregnant or breast feeding mothers
- Concurrent whole brain or craniospinal irradiation

TREATMENTS

DOSING AND ADMINISTRATION

Topotecan is supplied in 4 mg vials; the content of each vial is diluted in 4 ml of sterile water then further diluted with preservative free, pyrogen free saline to a final volume of 10 ml. Administration of the drug is performed at a constant rate of 2,0 ml/minute (total 5 minutes) through an intraventricular reservoir or lumbar puncture (LP).

The volume of CSF equivalent to the volume of drug to be administered is removed prior to drug administration.

Patients who receive topotecan via LP have to remain prone, flat or in the Trendelemburg position for 1 hour following drug administration. After drug administration via an intraventricular reservoir, the reservoir has to be flushed slowly for 1-2 minutes with approximately 2 ml of either CSF or preservative free normal saline then pumped 4-6 times.

Treatment:

• Induction: Topotecan IT 0,4 mg/dose twice weekly for 6 weeks

• Consolidation: Topotecan IT 0,4 mg/dose weekly for 4 weeks

• Maintenance: Topotecan IT 0,4 mg/dose twice monthly for 4 months then monthly through year 1

TREATMENT DURATION

The maximum planned treatment duration in absence of toxicity or progression is up to 2 years.

FOLLOW-UP

The follow-up period begins when the patient discontinues from study treatment.

If feasible, one post-discontinuation visit will be performed 30 days after treatment discontinuation and follow-up in all patients must be pursued every 2 months until the patient's death or up to at least one year until study cut-off.

Patients with adverse events at the end of the study related to treatment must be followed until recovery.

During post-therapy follow-up, information will be collected in the CRF regarding date of disease progression, further second line treatment (chemo, radiotherapy, surgery) and death. The date of first documented disease progression must be recorded on the CRF even if it occurs after the patient has started a new therapy. All deaths will be recorded.

TREATMENT DISCONTINUATION

Treatment should be discontinued if this is considered to be in the best interest of the patient. Treatment could be discontinued for the following reasons:

Investigator’s decision: if this decision is made because of toxicity, a serious adverse event, or a clinically significant laboratory value, appropriate measures will be taken and IGR will be notified immediately.

The patient, parents or legal representative’s refusal, withdrawal of patient consent.

The investigator or sponsor, for significant safety or efficacy reason, stops the study or stops the patient's participation in the study.

Evidence of progressive disease exists.

The patient becomes pregnant or fails to use adequate birth control (for those patients who are able to conceive).

The patient is non compliant with study procedures.

Life threatening toxicity.

Unmanageable or unacceptable toxicity, including the need for more than 2 dose reductions, except in cases of obvious patient benefit in continuing the treatment.

Treatment delay of more than 3 weeks for any reason except in cases of obvious patient benefit in continuing the treatment.

Study discontinuation, must be reported to IGR as soon as possible and immediately in case of discontinuation related to a serious adverse event. The primary reason and date of removal for all patients will be documented on the case report form (e.g. lost to follow-up, withdrawal of consent, patients wrongly included, adverse events, etc.). The final evaluation required by the protocol will be performed at the time of study discontinuation. Further follow-up should be reported. The investigator will attempt to complete all discharge procedures at the time a patient is removed from the treatment.

CONCOMITANT THERAPIES

Patients could receive chemotherapy to control systemic disease provided the systemic CT is not a phase I agent, doesn't significantly penetrate the CSF, or is not known to have serious unpredictable CNS side effects.

Patients are allowed to receive full supportive care therapies concomitantly during the study.

If during the study patient develops a need for palliative radiotherapy, it should be ensured that this is not a manifestation of progressive disease (patients with progressive disease must discontinue study therapy). Palliative radiotherapy may be given for control of pain or for other reasons with no curative intent. The irradiated area cannot be used as a parameter for response assessment.

EFFICACY AND SAFETY ASSESSMENTS

The following exams will performed according to the schedule of assessments after signature of written informed consent by patients or parents or legal representative.

CLINICAL ASSESSMENTS

Medical History

- Relevant past medical history, and current medical conditions not related to the current indication or disease for which patient entered into the study
- Information related to diagnosis of the disease under study
- Previous surgery, radiotherapy, systemic therapy, investigational therapy

Any disease related symptoms present at baseline.

Physical examination

- Physical and Neurological Examination
- ECOG Performance Status or Lansky-Play score
- Vital signs (pulse, blood pressure, temperature)
- Height, Weight and Body Surface

  Will be done within 7 days before study enrolment, then before each administration

LABORATORY AND TUMOR ASSESSMENTS

- CSF studies: cell count, differential, protein, glucose. CSF citology: at baseline and at each CT administration
- CT or MRI scans: at baseline, every 2 months and at the first post-discontinuation visit.
- MRI of the spine if clinically indicated.
- Bone marrow aspirates: at baseline
- Pregnancy test (urine or serum) in females of childbearing potential within 7 days before study enrolment.
- Complete Blood Count: leukocyte, neutrophil, platelets and haemoglobin within 7 days before study enrolment, then once a week during each cycle and every 2 days in case of neutro- or thrombocytopenia, and if possible at the first post-discontinuation visit
- Serum Biochemistry: sodium, potassium, calcium, total protein, creatinine, urea, AST (SGOT), ALT (SGPT), total bilirubin, albumin within 7 days before study enrolment, then once a week, and if possible at the first post-discontinuation visit.

SAFETY ASSESSMENTS

Adverse events are evaluated according to NCI common toxicity criteria (vers 3.0). Treatment has to be stopped if there is ≥grade 3 non hematologic toxicity considered to be at least possibly related to topotecan with the following exception: ≥grade 3 headache prevented after subsequent doses using premedication or >grade 3 nausea or vomiting that is well controlled or prevented after subsequent doses with antiemetics. After the routine use of dexamethasone patients with arachnoiditis could not receive further topotecan.

Any non hematologic toxicity experienced during a cycle must resolve to Grade 1 or lower before the next cycle may be administered.

CRITERIA FOR ASSESSMENT OF RESPONSE

Response is classified as complete response (CR), stable disease (SD) or progressive disease (PD).

For CR patients need to have complete clearing of malignant cells from lumbar or ventricular CSF on two consecutive citologic studies at least 4 weeks apart, with no worsening of physical or neurological findings clearly attributable to neoplastic meningitis; complete clearing of disease on two consecutive MRI scans >4 weeks apart.

PD is defined as the occurence of new malignant cells in the CSF on two consecutive occasions at least 1 week apart from after at least 3 previous consecutive negative CSF cytologist obtained at least 1 week apart or an increase of >25% in the size of measurable lesions on MRI or new lesions on MRI after a CR.

Patients are considered to have stable disease (SD) if they don't meet the criteria for either a CR or PD and without worsening of physical findings clearly attributable to disease.

ADVERSE EVENTS

It is of the utmost importance that all staff involved in the study are familiar with the content of this section. The principal investigator is responsible for ensuring this.

ADVERSE EVENT

Definition

An adverse event (AE) is the development of an undesirable medical condition or the worsening of a preexisting medical condition in a clinical investigation subject. The event need not necessarily have a causal relationship with study drug and can occur at any time, including run-in or wash-out periods, even if no study treatment has been administered. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, x-ray, ECG).

Recording of Adverse Events

When to collect AEs: any AE that occur from the time consent is given, during the study and in the 30 days following the last administration of study treatment should be recorded.

What AE to collect: all observed AEs regardless of treatment group or suspected causal relationship to study drug will be assessed following NCI-CTC Criteria and recorded on the AE page(s) of the CRF, and in case of serious adverse event in a SAE form too. Worsening/exacerbation of sign and symptoms (in terms of severity and/or frequency, or the appearance of new manifestations/complications) of the malignancy under study or of a pre-existing illness should be reported as AE in the appropriate section of the CRF.

Lack of or insufficient clinical response, benefit, efficacy, therapeutic effect, or pharmacological action, should not be recorded as an AE.

The investigator must make the distinction between exacerbation of preexisting illness and lack of therapeutic efficacy. In addition, clinically significant changes in physical examination findings and abnormal objective test findings (e.g., x-ray, ECG) should also be recorded as AE.

For all AEs, the investigator must pursue and obtain adequate information both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a SAE requiring immediate notification to IGR. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE (i.e., study drug or other illness). The investigator is required to assess causality and indicate that assessment on the CRF. All AEs and specially those that are serious, suspected to be related to study drug or considered significant by the investigator or clinical monitor must be followed after the time of therapy discontinuation until the event or its sequelae resolve or stabilize at a level acceptable to the investigator and the clinical monitor or his/her designated representative.

All AEs will be recorded in the Case Reporting Form (CRF).

SERIOUS ADVERSE EVENT

SAE definition

A Serious Adverse Event (SAE) is any adverse event occurring at any dose that:

· Is fatal (results in death).

· Is life-threatening.

· Requires or prolongs inpatient hospitalization.

· Results in persistent or significant disability/incapacity.

· Is a congenital anomaly/birth defect.

· Is medically significant or requires intervention to prevent one of the outcomes listed above.

Any clinical event or laboratory result considered serious by the investigator and not corresponding to the criteria of seriousness defined above is nevertheless considered to be medically significant. Such an event/result can carry a risk for the patient and can require medical intervention to prevent one of the outcomes listed above (i.e. overdoses, second cancer and pregnancies can be considered medically significant). Medical and scientific judgment should be exercised in deciding whether other situations such as important medical events that may not be immediately life-threatening or result in hospitalization but may jeopardize the safety of the patient or may require intervention to prevent one of the outcomes listed in the definition above.

A life-threatening AE is any adverse drug experience that places the patient/subject at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Hospitalization is defined as in-patient hospital admission associated with an AE which occurs or worsens after the patient has been included in study. Thus attendance/ treatment at an emergency room/outpatient department does not meet hospitalization SAE criteria. However, an event which results in attendance / treatment at such a facility is an SAE if it is considered medically significant or required intervention to prevent one of the other seriousness criteria.

Note: The SAE is the diagnosis or sign /symptom, NOT the procedure or test defined as any inpatient admission.

Inpatient admission in the absence of a precipitating, treatment-emergent, clinical AE may meet criteria for “seriousness” but is not an adverse experience and thus is not subject to immediate reporting to IGR.

Prolongation of hospitalization is defined as any extension of an inpatient hospitalization beyond the stay anticipated/required in relation to the original reason for the initial admission, as determined by the investigator or treating physician. For

protocol-specified hospitalizations in clinical trials, prolongation is defined as any extension beyond the length of stay described in the protocol. Prolongation in the absence of a precipitating, treatment-emergent, clinical AE (i.e., not associated with the development of a new AE or worsening of a pre-existing condition) may meet criteria for "seriousness" but is not an adverse experience and thus is not subject to immediate reporting to IGR. Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual patient/subject. Disability is a substantial disruption of a person's ability to conduct normal life functions.

SAEs reporting

Any SAE or SUSAR as defined above which occurs or comes to the attention of the investigator at any time during the study and through 30 days after the last administration of study drug, independent of the circumstances or suspected cause, must be reported immediately, within 24 hours of knowledge by fax via a SAE form.

The Pharmacovigilance Unit at IGR will assess the adverse events in terms of seriousness, expectedness (IB), severity (NCI-CTCAE v3.0) and relationship to the study drug. All SAEs will be coded using medDRA.

Assessment of causality of SAEs may be reviewed during the study by the study coordinator. Information collected in the SAE form is crucial to assess the case and for this reason diligence in collecting as much verifiable and reliable information: BOTH QUALITY and TIMELINES are key factors.

All SAEs should be reported immediately (within 24 hours of knowledge of the event), regardless of time elapsed since last study drug dose (until 30 days after the last administration of study drug). The investigator must provide any relevant information for the required 8 days follow up report for any SAE which is fatal or life threatening.

As far as possible, for each event, the following should be noted:

1. As clear as possible a description in medical terminology to allow for a complete medical assessment of the case and independent determination of possible causality
2. Its duration (start and end dates)
3. Action taken and the necessity for corrective treatment or not, stoppage of study drug(s) or not, and so on

4. Its intensity (grade 1-5), according to the NCI/NIH Common Terminology Criteria AE version 3.0 (a copy can be downloaded from the CTEP home page: http://ctep.info.nih.gov).

5. Its relationship to the study drug or treatment, the pathology treated, another pathology or another treatment, or to a constraint linked to the research (period without treatment, further tests required for the research, and so on). If causality is unknown and the investigator does not know whether or not study drug caused the event, it should be attributed to study drug. If the investigator's causality assessment is "unknown but not related to study drug", this should be clearly documented on study records.

6. Documentation of all co-medication and/or therapies

7. Documentation of all relevant medical history and/or co-existing diseases

8. The outcome (where applicable).

For non fatal events, developments should be followed up until either recovery or recovery of a previous state of health or until the stabilization of possible aftereffects. The investigator must also attach the following to the serious adverse event report form, wherever possible:

· A copy of the summary of hospitalization or prolongation of hospitalization

· A copy of the post-mortem report

· A copy of all laboratory examinations and the dates on which these examinations were carried out, including relevant negative results, as well as normal laboratory ranges.

· All other document that he judges useful and relevant.

All these documents will remain anonymous.

Further information can be requested (by fax, telephone or when visiting) by the monitor and/or the safety manager. All SAEs will be recorded in the Case Reporting Form (CRF) too.

Adverse events follow-up

The investigator is responsible for the appropriate medical follow-up of patients until resolution or stabilization of the adverse event or until the patient's death. This may mean that follow-up should continue once the patient has left the trial. Follow up information about a previously reported serious adverse event must be reported by the investigator to the pharmacovigilance unit within 48 hours of receiving it.

The investigator also transmits the final report at the time of resolution or stabilization of the SAE. He retains the documents concerning the supposed adverse event so that previously transmitted information can be completed if necessary.

Annual safety report

The pharmacovigilance unit at IGR will issue once a year throughout the clinical trial, or on request, the annual safety report (ASR) of the study, in accordance with the detailed guidance issued by the European Commission on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use of April 2006 and the applicable revisions thereof. The pharmacovigilance unit will send a copy of the ASR to the investigators and national sponsors. Each national sponsor should submit the ASR within 60 days of the data lock point (date of the first authorisation of the concerned clinical trial by a competent authority in a member state) to the national competent authority and the national Ethic Committee of the concerned Member State, according to national legislation.

STATISTICAL CONSIDERATIONS

TRIAL PLAN AND SAMPLE SIZE

ANALYSIS

DATA MANAGEMENT

DATA COLLECTION, QUALITY ASSURANCE, MANAGEMENT

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APPENDIX 1. PERFORMANCE SCALE AND LANSKY-PLAY SCALE

For children aged 1 to 12 years old, a play performance scale according to LANSKY is recommended.

ECOG Grade		Lansky-Play Scale	
0	Fully active, able to carry out all normal activity without restriction.	100	Fully active, normal.
		90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out light work.	80	Active, but tires more quickly.
		70	Both greater restriction of, and less time.
2	Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50 % of waking hours.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.
3	Capable of only limited self-care; confined to bed or chair more than 50 % of waking hours.	40	Mostly in bed; participates in quiet activities.
		30	In bed; needs assistance even for quiet play.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.	20	Often sleeping; play entirely limited to very passive actualities.
		10	No play; does not get out of bed.
5	Dead	0	Unresponsive

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COMUNICAZIONI ORALI

- Padova, 27-30.11.2009: *"Rabdomiosarcoma e adolescenti",* comunicazione orale al 65° congresso nazionale SIP.
- Padova, 3-4.12.2009: *"Il Rabdomiosarcoma negli adolescenti",* comunicazione orale durante la riunione annuale sui tumori solidi pediatrici, CSS di neuroblastoma, sarcomi delle parti molli, tumori rari, tumore di Wilms dell'AIEOP.
- Padova, 20.04.2010: *"Caso clinico sui tumori solidi in età pediatrica, i sarcomi delle parti molli",* tumor board del seminario sui tumori solidi in età pediatrica, i sarcomi delle parti molli, rivolto alla Scuola di Specializzazione in Pediatria dell'Università di Padova.
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