End-of-Life Care in Pediatric Neuro-Oncology

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Background. The management of children with cancer during the end-of-life (EOL) period is often difficult and requires skilled medical professionals. Patients with tumors of the central nervous system (CNS) with relapse or disease progression might have additional needs because of the presence of unique issues, such as neurological impairment and altered consciousness. Very few reports specifically concerning the EOL period in pediatric neuro-oncology are available. ***Procedure.*** Among all patients followed at our center during the EOL, we retrospectively analyzed data from 39 children and adolescents with brain tumors, in order to point out on their peculiar needs. ***Results.*** Patients were followed-up for a median time of 20.1 months. Eighty-two percent were receiving only palliative therapy before death. Almost half the patients (44%) died at home, while 56% died in a hospital. Palliative sedation with midazolam was performed in 58% of cases; morphine was administered in 51.6% of cases. No patient had uncontrolled pain. ***Conclusions.*** The EOL in children with advanced CNS cancer is a period of active medical care. Patients may develop complex neurological symptoms and often require long hospitalization. We organized a network-based collaboration among the reference pediatric oncology center, other pediatric hospitals and domiciliary care personnel, with the aim to ameliorate the quality of care during the EOL period. In our cohort, palliative sedation was widely used while no patients died with uncontrolled pain. A precise process of data collection and a better sharing of knowledge are necessary in order to improve the management of such patients. Pediatr Blood Cancer

Key words: brain cancer; end-of-life; neuro-oncology; palliative care; pediatric oncology; supportive therapy

INTRODUCTION

Central nervous system (CNS) tumors account for roughly 25% of all pediatric neoplasms [1]. Prognosis depends on the tumor site, chemo- and radiosensitivity, surgical radicality, presence of metastases, and the patient's age. Despite improvements in treatment, the outcome for some patients remains dismal: 5 year overall mortality in Europe is estimated at around 35% [2,3].

Children with CNS tumors who relapse or go through disease progression have to cope with unique problems that are not normally present in most other patients, such as focal neurological deficits, paralysis, cognitive deterioration, behavioral alterations, dysphagia, dysarthria, and dysphasia. Such symptoms strongly affect quality of life even in the absence of pain and dyspnea.

Literature specifically concerning end-of-life (EOL) care in children with CNS cancer is very limited. One of the most relevant studies was published by a Canadian group [4] and describes a cohort of children and adolescents with CNS cancer, albeit from a psychological point of view. Another study, carried out on 169 adults, describes the major clinical problems that affect CNS cancer patients during the EOL period, the most frequent issues being seizures (30% of patients), headache (36%), dysphagia (85%), death rattle (12%), drowsiness (85%), agitation and delirium (15%), steroid-associated hyperglycemia (10%) and psychosis (4%) [5].

In our paper, we analyze the major issues in EOL care in children with CNS tumors treated at our Center.

METHODS

Clinical data were collected retrospectively for all children and adolescents with a diagnosis of CNS cancer, who were followed-up at the "Regina Margherita" Children's Hospital in Turin (Italy) and who died between January 2005 and December 2011. We excluded cases which were followed-up elsewhere and came to our center only for surgery or for an oncology consultation. We excluded one patient with a brain tumor who developed a myelodysplastic syndrome and died as a result of hematological progression. A total of 39 patients were included in this study.

Master data, the date of start-therapy and stop-therapy, the date of diagnosis, relapse and death were obtained from our hospital database. The spreadsheet resulting from the database query was complemented by clinical data about symptoms, neurological impairment, medications, psychological issues, pain, etc., that were obtained from patients' digital or paper records archived at our institution.

When patients received part of their EOL care in other hospitals, physicians from such institutions were contacted by our center in order to obtain updated clinical data. For patients who received much of their EOL care at home, the parents communicated by phone any relevant clinical change. Nonetheless, the collection of precise information depends mainly on the family's compliance. Data are complete in 25–39 patients. The incomplete data relate

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mainly to pharmacological therapy of patients who spent a number of weeks at home or in other hospitals before dying. In Tables IV and V, the extent of missing data is declared.

At our unit, when a patient cannot receive further curative treatment, the oncologist and psychologist organize a meeting with the family (and often with the patient, though in a dedicated and separate setting) to propose a path of palliative care. In this manuscript, we considered that moment as the initiation of palliative therapy. We also use in this paper expressions, such as palliative care or palliation period, that are referred to as the time period that follows the decision to avoid further antineoplastic treatment with curative intention. While it is possible to state when the palliative care begins, the starting moment of the "end-of-life" is difficult to define. Scientific evidence does not support defining the end of life as crossing an arbitrary threshold. Some patients could be in their EOL period before entering a palliative care program (such as patients 1, 2, and 35) while others started palliative therapy long before being considered terminally ill (such as patient 38).

During the palliative period, low-dose chemotherapy may be administered (e.g., oral etoposide), in order to delay disease progression, but sometimes also to comply with the patient's desire not to interrupt all therapies. In the very last days or weeks of life, especially if a patient develops dysphagia or coma, such therapy is usually discontinued.

The Regional Pediatric Oncology Network

Within our region (Piedmont), medical care for children with cancer is organized in the Piedmont Pediatric Oncology Network, which is structured according to a hub-and-spoke model. The pediatric oncohematology unit is located in the reference children's hospital, in Turin.

Nine "spokes" are located throughout the region. Each one can provide adequate facilities and expertise for children with cancer. Spokes are further classified into three-second-level units (with isolated rooms, nurses with skills in pediatric oncology, and facilities to prepare and administer chemotherapy) and six-first-level units (with essential facilities). In both first and second level units, children can receive supportive care between chemotherapy courses or during disease progression. Decisions concerning the most delicate phases of the disease (diagnosis, progression, relapse, palliation) are always discussed in agreement with the "hub" oncohematology unit.

At the Regina Margherita hospital in Turin, all pediatric oncologists are trained in the field of palliative care. L.S., who coauthored this paper, is the referent for palliative care at our center and is actively involved in the activity of the Regional Network of Palliative Care (active in Piedmont since 2010).

The hub promotes the organization of educational events (meetings, seminars, small conferences) that can either be opened to all professionals or dedicated to a certain group of people (e.g., physicians, nurses, psychologists, etc.) within the network. Such events are mainly focused on supportive therapy, social and psychological matters, the roles of family doctors, and, of course, palliative care. Furthermore, selected nurses from spokes spend training periods at the pediatric oncohematology facility in Turin. Active and lively cooperation has been established during the last years among all professionals of the network.

RESULTS

Thirty-nine patients who were followed at our center and who died between January 2005 and December 2011 were included in the study. Patients are equally distributed among males (20) and females (19). The median age at diagnosis was 5.7 years (range 4 months – 16 years). Median age at death was 8.3 years (range 14 months – 17 years). The median duration of the patients' clinical history (defined as the time between diagnosis and death) was 20.1 months, but the range was extremely wide (2.4–149.9 months). The histology is detailed in Table I.

Previous Treatment

All patients received disease directed treatment with curative intent prior to being treated in a palliative care setting. Thirty-four patients (87%) underwent neurosurgery at least once (major surgery or biopsy). Thirty-one patients (79%) received radiotherapy. All patients underwent chemotherapy. Details of surgery, chemo- and radiotherapy are reported in Table II.

Terminal Hospitalization

In our cohort, 22 patients (56%) died in a hospital. In the reference hospital, 13 patients died in the oncohematology department three in other departments (in the emergency, respiratory disease, and intensive care units). Six patients died in the pediatric oncology network's other "spoke" hospitals. Seventeen patients (44%) died at home.

In 33–39 patients, death was an expected event. Nonetheless, some patients were still receiving chemotherapy during the last month of life. Three patients (7.7%) were in first-line treatment, one patient (2.6%) was receiving second-line therapy, two patients (5.1%) were having oral metronomic therapy. One patient (2.6%) was in a wait and see phase. The majority of patients (32 out of 39, 82.1%) were receiving supportive care, but were not receiving any type of chemotherapy, and no further anti-neoplastic treatment had been planned for them.

Neurological Impairment

Twenty-seven patients (69.2%) had at least one relevant cranial nerve deficit during the last month of life. The most frequently involved were the facial, abducent and oculomotor nerves. Five children (13%) had partial or complete visual impairment. Twelve children (30.8%) had gait difficulties at diagnosis. During EOL, the percentage had doubled (24 patients, 68.6%). Fourteen patients (41%) needed lengthy bed rest (at least 30 consecutive days), either at home or during hospitalization, before death. This was caused by paraplegia, tetraplegia, or by deterioration of consciousness and psycho-cognitive skills.

Common Supportive Measures

At our center, during the EOL period, all patients can benefit from basic supportive measures such as neuromotor rehabilitation, antifungal or antibiotic therapy (administered only in case of the presence of infection-related symptoms that cause pain or discomfort) and non-invasive oxygen therapy. Furthermore, psychological and social support is offered to all patients and families in the setting of a multidisciplinary approach.

TABLE I. Patients' Characteristics

Patient	Sex	Pathology	Age at diagnosis	Age at death	History duration (months)
1	F	MB	13.3	13.5	2.4
2	M	MB	4.1	4.4	3.2
3	M	MB	2.0	2.2	3.3
4	M	DIPG	4.9	5.2	3.8
5	F	Diffuse astrocytoma	9.5	9.9	3.9
6	M	DIPG	5.7	6.1	4.8
7	M	DIPG	2.9	3.4	6.0
8	F	DIPG	6.5	7.2	8.4
9	F	DIPG	12.0	12.8	9.3
10	M	DIPG	16.6	17.4	9.5
11	F	Pinealoblastoma	0.4	1.2	9.7
12	F	DIPG	12.6	13.4	9.9
13	M	stPNET	2.2	3.0	10.3
14	F	DIPG	13.0	14.1	13.4
15	M	GB	7.2	8.3	13.4
16	M	AT/RT	13.6	14.8	13.8
17	M	stPNET	1.6	2.8	14.6
18	F	GB	7.7	9.0	15.2
19	F	GB	5.8	7.3	17.6
20	F	GB	4.8	6.5	20.1
21	M	Diffuse astrocytoma	8.6	10.4	22.2
22	F	Anaplastic astrocytoma	3.6	5.4	22.2
23	M	Anaplastic astrocytoma	7.7	9.7	24.2
24	M	MB	3.1	5.3	26.4
25	M	stPNET	11.3	13.7	28.1
26	F	Ependymoma	0.8	3.2	28.6
27	M	MB	5.7	8.2	29.7
28	M	Diffuse astrocytoma	2.4	5.0	31.2
29	F	MB	4.2	6.8	31.3
30	F	MB	4.9	8.1	38.1
31	F	Pinealoblastoma	10.0	13.5	42.5
32	M	Germ cell tumor	10.4	14.4	47.7
33	M	MB	4.3	8.6	51.7
34	M	Ependymoma	13.1	17.6	54.2
35	M	Craniopharyngioma	4.7	11.0	76.3
36	F	MB	8.5	15.5	83.5
37	F	I grade astrocytoma	0.3	7.4	85.2
38	F	I grade astrocytoma	8.1	15.8	91.7
39	F	Ependymoma	4.3	16.8	149.9
		Min	0.3	1.2	2.4
		Max	16.6	17.6	149.9
		Median	5.7	8.3	20.1

MB, medulloblastoma; stPNET, supratentorial primitive neuroectodermic tumor; AT/RT, atypical teratoid/rhabdoid tumor; DIPG, diffuse instrinsic pontine glioma; GB, glioblastoma.

Thirty-four patients out of 39 had a central venous catheter (CVC) during the last month of life. Three had a Port-a-cath [6] (7.7%); 28 had a Broviac-Hickman [7] (71.8%); 3 had a PICC [8] (Peripherally Inserted Central Catheter, 7.7%). Five patients (12.8%) did not have any CVC.

All patients who were treated with palliative intention received electrolyte support and sometimes, intravenous dextrose solution; only three patients received total parenteral nutrition (TPN) during the last month of life.

Pharmacological Management

Data concerning the use of steroids, mannitol, morphine, midazolam, and antiepileptic drugs for 31 patients are detailed in Table IV. Twenty-six patients (83.8%) received steroidal drugs as part of their palliative therapy. Dexamethasone was used in all cases, and in 18 patients it was administered for more than 60 days (minimum time: 14 days). All patients who received dexamethasone chronically developed at least one related collateral effect (cushingoid facies, weight gain, hypertension, hyperglycemia, irritability, insomnia). Among our patients, only two out of 31 patients (6.4%) received mannitol during EOL. Mannitol was administered for 50 days in the first patient and 14 days in the second patient.

Benzodiazepines can be used to alleviate anxiety or to induce pharmacological sedation. Eighteen patients (58%) were pharmacologically sedated for periods ranging between one and 67 days before death (median 9 days). Midazolam was the drug of choice in

TABLE II. Previous Treatments

Pt	Disease	Chemotherapy	Auto-HSCT	Therapy lines	RT	Major surgery or biopsy	VPS or VCS
1	MB	HART	No	1	—	1	Yes
2	MB	HART	No	1	—	1	No
3	MB	PNET INFANTS	No	1	—	1	Yes
4	DIPG	Temozolomide, CDDP/VP16	No	2	—	1	No
5	Diffuse astrocytoma	HGG OIRM	No	1	Local	1	No
6	DIPG	Temozolomide	No	1	Local	0	No
7	DIPG	Temozolomide	No	1	Local	0	No
8	DIPG	Temozolomide	No	1	Local	0	No
9	DIPG	Temozolomide	No	1	Local	0	No
10	DIPG	Temozolomide + VP16 + bevac/irinot	No	3	Local	1	No
11	Pinealoblastoma	BB-SFOP, AIEOP HIGH RISK INFANTS	Yes	2	—	1	Yes
12	DIPG	HGG OIRM	Yes	1	Local	0	No
13	stPNET	Infants + RT	Yes	2	Local	1	Yes
14	DIPG	Temozolomide + VP16	No	2	Local	1	Yes
15	GB	Temozolomide + HGG OIRM	No	2	Local	2	No
16	AT/RT	HART	Yes	1	CSI	1	No
17	stPNET	PNET Infants + 8in1 + temozolomide	Yes	3	—	1	Yes
18	GB	HGG OIRM + Temozolomide	Yes	2	Local	1	No
19	GB	HGG OIRM + vinorelbine	Yes	2	Local	3	Yes
20	GB	HGG OIRM + Temozolomide	Yes	2	Local	2	No
21	Diffuse astrocytoma	LGG2004 + temozolomide	No	2	Local	1	Yes
22	Anaplastic astrocytoma	HART + 2 courses Bevac and irinotecan	Yes	2	Local	2	Yes
23	Anaplastic astrocytoma	Temozolomide + Bevac/ irinot + VP16 + Vinorelbina/valproato	No	4	Local	1	No
24	MB	INFANTS, Temozolomide	No	2	CSI	1	Yes
25	stPNET	HART, Temozolomide	Yes	2	CSI	1	No
26	Ependymoma	INFANTS + VP16	Yes	2	Local	2	No
27	MB	PNET4 + HGG OIRM + Temozolomide	No	3	CSI	1	Yes
28	Diffuse astrocytoma	LGG2004	No	1	—	1	Yes
29	MB	AIEOP SNC99-AR	Yes	1	CSI	1	Yes
30	MB	AIEOP SNC99-AR + 8in1	Yes	2	CSI	1	Yes
31	Pinealoblastoma	AIEOP SNC99-AR + HGG OIRM+ 8 in 1 + temozolomide	Yes	4	CSI	1	Yes
32	Germ cell tumor	CNS-CGTII, CNS-GCTII-HR, 2 courses CE, VP16	Yes	4	CSI	4	No
33	MB	HART, 8 IN 1,VP16	Yes	3	CSI	1	Yes
34	Ependimoma	Protependymomas, temozolomide	No	2	Local	7	Yes
35	Craniopharyngioma	CT (low doses), radiosurgery	No	2	Local	10	Yes
36	MB	AIEOP SNC99 AR, Vinorelbine/ temozolomide, VP16, cyber-knife, radiosurgery	Yes	5	CSI	3	Yes
37	I grade astrocytoma	LGG2004, temozolomide, bevacizumab	No	3	—	1	No
38	I grade astrocytoma	LGG2004, temozolomide	No	2	Local	2	Yes
39	Ependymoma	Prot. ependymomas, temozolomide, brachytherapy, VP16, Vinorelbine + gliadel, chloroquine, nimotuzumab	No	6	Local	8	Yes

MB, medulloblastoma; stPNET, supratentorial primitive neuroectodermic tumor; AT/RT, atypical teratoid/rhabdoid tumor; DIPG, diffuse intrinsic pontineglioma; GB, glioblastoma; AutoHSCT, autologous hematopoietic stem cell transplantation; RT, radiotherapy; CSI, craniospinal irradiation; VPS, ventriculo-peritoneal shunt; VCS, ventriculocisternostomy; HART, intensive protocol encompassing metotrexate; VP16, carboplatin, cyclophosphamide +/− vincristine, hyperfractioned accelerated radiotherapy for stPNET and high-risk medulloblastomma. OIRM HGG: intensive protocol for HGG developed at our Institution. PNET4: conventional intensity protocol for standard-risk medulloblastoma. INFANTS: intensive chemotherapy protocol for PNET and MB in children younger than 3 years. CNS GCT, germ cell tumor protocol; AIEOP SNC99AR, high intensity protocol for high-risk MB developed in Turin; LGG2004, low-grade glioma protocol.

all patients who underwent palliative sedation (defined as the practice of relieving distress in a terminally ill patient in their last hours or days of life, usually by administering a sedative drug by continuous infusion). In our cohort, dyspnea and terminal agitation were the most frequent indications for terminal sedation (as reported in Table IV). Sixteen patients (51.6%) received morphine for a time period ranging between one and 584 days (median 14.5 days). Thirteen patients (41.9%) had seizures during their

TABLE III. Neurological Deficits

Pt	Cranial nerve deficits in the last month of life	Gait disorder at diagnosis	Gait disorder in the last month of life	Bedrest > 30 days before death	Invalidity in the last month of life
1	VI, VII, VIII	Yes	Yes	No	Left ear deafness
2	—	Yes	Yes	No	Lower limb paresis
3	III	No	Yes	No	Coma
4	—	Yes	Yes	Yes	Mental retardation; obesity (congenital)
5	—	Yes	Yes	Yes	Upper limbs paresis
6	VI	No	No	No	Diplopia, gait deficits
7	VI, VII, XII	No	No	No	Urinary incontinence
8	III	No	No	No	Left eye exotropia
9	VI, VII, XII	No	No	No	Cranial nerves
10	VII	No	Yes	Yes	Paraplegia
11	I	Yes	Yes	Yes	Amaurosis, spastic tetraplegia
12	V, VII, VIII	Yes	Yes	No	Gait deficit
13	—	Yes	Yes	Yes	Sphincter disorder
14	VI, VII, V, XII	No	Yes	Yes	Dysphagia
15	I	No	Yes	No	Amaurosis
16	I	No	No	No	Vision loss
17	—	No	Yes	Yes	Drowsiness
18	VII	No	No	Unknown	—
19	VII, III	No	No	Unknown	—
20	VII	No	Yes	No	Hemiplegia
21	I	Yes	Yes	No	Facio-crural weakness
22	VI, VII, VIII	No	Yes	No	Dysphagia
23	VI,III,VIII	No	No	No	Dysmetria
24	—	No	Unknown	Unknown	unknown
25	VIII	Yes	Unknown	Unknown	unknown
26	—	No	Unknown	Unknown	unknown
27	—	No	Unknown	No	unknown
28	—	No	No	No	—
29	VII, V, III, VI	Yes	Yes	Yes	Posterior cerebral fossa syndrome
30	—	No	Yes	Yes	Paraplegia
31	—	No	Yes	Yes	Paraparesis
32	VII, VIII, V	No	Yes	No	Paraplegia
33	VII	No	Yes	No	Paraplegia
34	—	No	No	No	—
35	VII	No	Yes	Yes	Coma
36	VII, VIII	No	Yes	No	Paraparesis
37	I	Yes	Yes	Yes	Tetraparesis
38	VII, III	Yes	Yes	Yes	Paraplegia, dysphagia
39	I	No	No	Yes	Paraplegia, coma

clinical history, and 20 children overall (51.2%) received anti-epileptic drugs during the last month of life.

Hospitalization

Among our patients, 22 (56%) died in a hospital. The length of the last hospitalization ranged from one to 90 days, with a median time of 22.5 days. In 28 patients, we calculated the number of days of pure palliation intended as the time period during which the patient received supportive treatment, but no specific antineoplastic drugs, the median period was 36 days (range: 0–1,166). The patient with the longest palliation period (1,166 days) was a female with a low-grade glioma, who was diagnosed at the age of eight and died at 15. She had interrupted antineoplastic drugs for over 3 years before death and eventually died as a result of respiratory failure after multiple pulmonary infections. She also received opioids for the longest period among our patients (584 days).

Psychological Support

Nine patients (23%) were followed by the psycho-oncology service at our hospital. The age range for those patients was 6.8–17.6 years (median 14.4). The patients' parents also often needed psychological support. Out of 39 families, 10 (at least one parent or at least a first-degree relative, 25.6%) were followed-up by the psycho-oncology service. In six cases, psychologists followed-up the family but not the patient. In four cases, only the patient was supported. In four cases, both the family and the patient received psychological support.

TABLE IV. Drugs Used for Supportive Therapy During the End-of-Life Period (Data Available for 31 Patients)

Pt	Dexamethasone	Days of dexamethasone before death (days)	Mannitol	Days of mannitol before death (days)	Midazolam	Days of midazolam before death (days)	Indication for terminal sedation (midazolam)	Morphine	Days of morphine before death (days)	Seizures	Anti-epileptic prophylaxis or therapy
1	No	—	No	—	No	—		No	—	No	No
2	Yes	>60	No	—	No	—		No	—	Yes	No
3	Yes	17	No	—	Yes	16	Terminal agitation	Yes	15	No	No
4	Yes	>60	No	—	No	—		No	—	No	No
5	Yes	>60	No	—	Yes	9	Dyspnea	No	—	Yes	Yes
8	Yes	14	No	—	Yes	2	Seizures	Yes	1	Yes	Yes
9	Yes	>60	No	—	Yes	14	Dysphagia, terminal agitation	Yes	14	Yes	Yes
10	Yes	>60	No	—	Yes	2	Dyspnea	Yes	3	No	No
11	Yes	>60	No	—	No	—		No	—	Yes	Yes
12	Yes	>60	Yes	14	Yes	1	Dyspnea	No	—	No	No
13	Yes	>60	No	—	Yes	67	Dysphagia, agitation	Yes	90	No	Yes
14	Yes	>60	No	—	Yes	36	Seizures, dysphagia	Yes	32	Yes	Yes
15	No	—	No	—	Yes	23	Seizures, agitation	No	—	Yes	Yes
16	Yes	60	No	—	No	—		No	—	No	Yes
17	Yes	63	Yes	50	Yes	22	Dyspnea	Yes	53	Yes	Yes
20	Yes	>60	No	—	No	—		No	—	No	Yes
21	Yes	>60	No	—	Yes	1	Seizures, terminal agitation	No	—	Yes	Yes
22	Yes	30	No	—	Yes	8	Dyspnea	Yes	8	No	No
23	Yes	37	No	—	Yes	14	Seizures	Yes	14	Yes	Yes
27	Yes	10	No	—	Yes	6	Terminal agitation	Yes	6	No	No
28	No	-	No	—	No	—		No	—	No	No
29	Yes	>60	No	—	Yes	9	Dyspnea	Yes	9	No	No
31	Yes	60	No	—	Yes	14	Dyspnea	Yes	20	No	Yes
32	Yes	>60	No	—	No	—		Yes	30	Yes	Yes
33	Yes	>60	No	—	Yes	2	Dyspnea	Yes	20	No	Yes
34	Yes	>60	No	—	Yes	1	Dyspnea, terminal agitation	No	—	Yes	Yes
35	No	—	No	—	No	—		No	—	No	No
36	Yes	19	No	—	No	—		No	—	No	Yes
37	Yes	>60	No	—	No	—		Yes	7	No	Yes
38	No	—	No	—	No	—		Yes	584	Yes	Yes
39	Yes	>60	No	—	No	—		No	—	No	Yes

DISCUSSION

Our study provides a detailed description concerning the EOL care of a group of children with CNS cancer treated in a single center. Our data are limited by the retrospective nature of our study, and by the fact that some of the information concerning children who died at home or in other hospitals is not complete. For all patients, the EOL continued to be a period of active medical care, requiring multiple medical and nursing interventions and relevant social and psychological support.

The majority of patients (82%) had interrupted all anti-neoplastic treatments before dying. This differs somewhat from what has been reported in previous studies in both children and adults [9,10], in which the percentage was around 40%. The frequency of neurological deficits among patients with CNS cancer (dysphagia and coma in particular) could partly explain the fact that so many patients were not receiving antineoplastic therapy at the EOL. Physicians and parents are more easily prone to discontinue chemotherapy if the patient's consciousness is impaired or if it becomes impossible to administer oral drugs.

Twenty-five patients in our cohort received more than one line of chemotherapy, and many also underwent surgery and radiotherapy. Forty-three percent of the patients underwent autologous hematopoietic stem cell transplantation. It does not seem that our children were over-treated. Indeed, there was a median of two chemotherapy lines and a median of one major surgical operation. There are, however, some outliers, such as one patient who received six different types of chemotherapy and one patient who underwent surgery 10 times. Whenever possible, over-treatment should be avoided, though it is sometimes the result of a mediation between physicians and parents [10].

The presence of a regional pediatric oncology network helped provide all patients adequate treatment in the setting of palliative care. "Spokes" are widely distributed throughout the region and are easily reachable in minutes even by patients who live in remote areas, allowing them to be hospitalized and followed near home. Being hospitalized near to one's home can help maintain contact with friends and family members. For the parents and caregivers, economic and logistic problems are simplified. Physicians and nurses from the spoke unit can keep in touch easily with the parents, the family doctor, and/or the domiciliary care units.

Seventeen patients died at home (43.5%); in previous reports that percentage was between 23% and 40% [9]; in a French cohort almost 75% of patients received supportive care at home [11]. At our center, all efforts are made in order to facilitate the domiciliary care of patients at the EOL. If the patient's clinical conditions allow hospital discharge, our proposal to the family is to administer palliative care at home. If the family accepts to start domiciliary care and if the child's consciousness is still preserved, we share the decision with the patient (with modalities that fits the patient's age

TABLE V. Summary Data

General data (available for 39 patients)	
Males	20 (51%)
Females	19 (49%)
Median age at diagnosis	5.7 years
Minimum and maximum age at diagnosis	4 months–16 years
Median age at death	8.3 years
Minimum and maximum age at death	14 months–17 years
Median duration of clinical history	20.1 months
Minimum and maximum duration of clinical history	2.4–149.9 months
Antineoplastic treatment (data available for 39 patients)	
Patients who underwent major surgery or biopsy at least once	34 (87%)
Median number of neurosurgical interventions per patients	1
Patients who underwent VCS or VPS	21 (53%)
Patients who underwent radiotherapy	31 (79%)
of whom: local RT	21
of whom: CSI	10
Patients who received chemotherapy	39 (100%)
Patients who underwent auto-HSCT	17 (43.6%)
Median number of medical lines of treatment per patient	2
Lowest and highest number of medical lines of treatment per patient	1–6
Death location (data available for 39 patients)	
Patients who died in a hospital	22 (56%)
Patients who died at home	17 (44%)
Patients who were in "pure palliation" when they died	32 (82.1%)
Hospitalization	
Median number of days of "pure palliation" (data available for 28 patients)	36
Minimum and maximum number of days of "pure palliation" (data available for 28 patients)	0–1166
Median number of days of hospitalization before death (data available for 16 patients who died in a hospital)	22.5
Minimum number of days hospitalization before death (data available for 16 patients who died in a hospital)	1–90
Psychological support (data available for 39 patients)	
Patients who received psycho-oncologic support	9 (23%)
Family member(s) who received psycho-oncologic support	10 (25.6%)
Median death age of patients followed-up by psychologists	14.4 years
Age range of patients followed-up by psychologists	6.8–17.6 years

Auto-HSCT, autologous hematopoietic stem cell transplantation; CSI, craniospinal irradiation; RT, radiotherapy; VCS, ventriculocisternostomy; VPS, ventriculo-peritoneal shunt.

and psychological status). In our cohort, each of the families of the 17 patients, who died at home, had declared their will receive domiciliary care until death.

The cooperation with the hospitals of the regional oncohematology network and with family doctors may have been beneficial in the management of patients treated at home. Sometimes it was not possible to arrange adequate domiciliary support, thus some patients needed to be hospitalized. The duration of the hospitalization, before death, ranged from one to 90 days, with a median of 22.5 days.

A minority of patients received parenteral nutrition (9%) during EOL. While avoiding medically assisted parenteral hydration and nutrition is widely accepted in the USA [12], this is more difficult in Italy, where some families and doctors still consider therapeutic abstention as forced fasting that may accelerate or cause a patient's death [9].

In our cohort, only five patients (12.8%) were not carrying a CVC when they died. EOL care often requires a central venous access, and this is especially true in patients with brain cancer who often need antiemetic therapy, develop dysphagia, and the use of peripheral venous access can be difficult because of the cushingoid state of many patients during chronic steroidal therapy.

The most commonly used drugs in palliative care in pediatric neuro-oncology are corticosteroids, diuretics, opioids, and

sedative-hypnotics. In our cohort, 83.8% of patients received steroids; only 6.4% were administered mannitol, 58% needed palliative sedation, and 51.6% received morphine. Opioids are the mainstay for pain treatment in both adults and children. A retrospective study shows that among patients needing antalgic treatment, opioid therapy was completely effective in 27% of cases [13].

In our cohort, no patient had uncontrolled pain. There are obvious limitations in assessing pain control in patients with progressive neurological and cognitive impairment. In our cohort, physicians and nurses assessed pain in hospitalized children, while parents estimated the presence of pain when the patients were receiving domiciliary care. Pain scales were not routinely used. The collection of data concerning pain assessment relied on the description of the patients' symptoms, as reported in the clinical records. As a result of such limitations, though no case of persistent uncontrolled pain was described among our patients, we cannot exclude that the presence of pain might have been underestimated. Symptoms vary among different disease groups in pediatric oncology. While neurological deficits are more frequent in patients with brain cancer [9], the presence of uncontrolled pain is more frequent in other diseases (such as sarcomas). In patients with CNS cancer, extra-neural metastases are rare. Pain is represented mainly by headache, and is often controlled by steroids. Neurological symptoms such as dysphagia, diplopia, dysarthria, and coma are the most challenging issues in the very last days of life. Palliative sedation with midazolam is useful in such situations, while morphine is more widely used in patients with conserved consciousness who complain of visceral or bone pain. We reviewed our patients' records in order to check whether the use of midazolam was related to the presence of uncontrolled pain, but we found that indications for palliative sedation (as reported by the prescribing physicians) were dyspnea, agitation, seizures, and dysphagia.

The use of morphine and midazolam is complementary rather than additional during EOL. We might speculate that in situations requiring an earlier and wider use of terminal sedation (such as in pediatric neuro-oncology), the patients' need for opioids is lower than expected. Indeed, a paper published in 2009, including 1,466 children with cancer treated in 33 hospitals across the USA, showed that 56% of patients received therapy with opioids in the last week of life [14], but patients with brain tumors were treated with opioids in half the cases of leukemia patients and in a third of sarcoma patients.

The use of benzodiazepines for palliative sedation was discussed in a 2007 paper reporting on 19 children with CNS tumors and sarcomas [15], who died between 2000 and 2006. The median sedation time was 9.5 hours (range 7–288 hours). Refractory pain, hemorrhage, dyspnea, and seizures are obvious and universally accepted indications for the use of benzodiazepines in palliative medicine. Indeed, it is much more difficult to support the practice of sedation in cases of anxiety, severe depression, fear. and anguish. In such cases, antidepressants might be used on the basis of a psychiatric consult. In North America, the use of selective serotonin reuptake inhibitors (SSRIs) is widespread [16]. In Europe, particularly in Italy, antidepressants are not routinely included in the integrated palliative approach in pediatric oncohematology [17]. None of our patients were treated with antidepressants during the last month of life. The use of psychotropic drugs (in particular SSRI and benzodiazepines) might improve our approach in the management of adolescents and children during EOL.

The improvement in quality of EOL care in pediatric oncohematology derives from an improvement in skills among healthcare professionals and a better availability of territorial and home care providers. Though our paper is mainly focused on medical care, we believe that an interdisciplinary approach is of fundamental importance in all fields of palliative therapy, and not only in pediatric neuro-oncology.

By presenting our experience, we stressed the importance of the continuity of care, resulting from the organization of a good health-care network for children with cancer. We had no patients with persistent uncontrolled pain and we managed to provide palliative care at home for more than 40% of patients. Nonetheless, we believe that our results might be further improved. In the near future, we will focus in particular on the development of a prospective process of data collection and of shared algorithms for the pharmacological therapy. We plan to invest further in sharing knowledge across our network and in improving the coordinated action among hub hospitals, peripheral units, and domiciliary services.

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REFERENCES

1. Fleming AJ, Chi SN, Brain tumors in children. Curr Probl Pediatr Adolesc Health Care 2012;42:80–103.
2. Magnani C, Pastore G, Coebergh JW, et al. Trends in survival after childhood cancer in Europe, 1978–1997 : Report from the Automated Childhood Cancer Information System project (ACCIS). Eur J Cancer 2006;42:1981–2005.
3. Gatta G, Capocaccia R, Stiller C, et al. Childhood cancer survival trends in Europe: A eurocare working group study. JCO 2005;23:3742–3751.
4. Zelcer S, Cataudella D, Cairney AEL, et al. Palliative care of children with brain tumors: A parental perspective. Arch Pediatr Adolesc Med 2010;164:225–230.
5. Pace A, Lorenzo CD, Guariglia L, et al. End of life issues in brain tumor patients. Journal of Neuro-Oncology 2008;91:39–43.
6. PORT-A-CATH® Implantable Venous Access Systems [Internet][cited 2012 Aug 10]. Available from: http://www.smiths-medical.com/catalog/implantable-ports/port-cath-implantable-venous.html
7. Hickman®/Broviac®/Leonard® Catheters | Central Venous Catheters | Bard Access Systems [Internet][cited 2012 Aug 10]. Available from: http://www.bardaccess.com/picc-hick-brov-leon.php?section=Overview
8. Medcomp® | Pro-PICC® CT Injectable Catheters [Internet][cited 2012 Aug 10]. Available from: http://www.medcompnet.com/products/piccs/
9. Cohen-Gogo S, Marioni G, Laurent S, et al. End of life care in adolescents and young adults with cancer: Experience of the adolescent unit of the Institut Gustave Roussy. Eur J Cancer 2011;47:2735–2741.
10. Harrington SE, Smith TJ., The role of chemotherapy at the end of life: "When is enough, enough?" JAMA 2008;299:2667–2678.
11. Schell M, Castaing M., Isolated health professionals in paediatric palliative care. Arch Pediatr 2006;13:625–628.
12. Geppert CMA, Andrews MR, Druyan ME., Ethical issues in artificial nutrition and hydration: A review. JPEN 2010;34:79–88.
13. Wolfe J, Grier HE, Klar N, et al. Symptoms and suffering at the end of life in children with cancer. New Engl J Med 2000;342:326–333.
14. Orsey AD, Belasco JB, Ellenberg JH, et al. Variation in receipt of opioids by pediatric oncology patients who died in children's hospitals. Pediatr Blood Cancer 2009;52:761–766.
15. Postovsky S, Moaed B, Krivoy E, et al. Practice of palliative sedation in children with brain tumors and sarcomas at the end of life. Pediatr Hemat Oncol 2007;24:409–415.
16. Kersun LS, Kazak AE., Prescribing practices of selective serotonin reuptake inhibitors (SSRIs) among pediatric oncologists: A single institution experience. Pediatr Blood Cancer 2006;47:339–342.
17. Clerici CA, Simonetti F, Massimino M, et al. Antidepressants in pediatric oncology. Pediatr Blood Cancer 2008;50:1290–1291