


Children and adolescent solid tumours and high-intensity end-of-life care: what can be done to reduce acute care admissions?

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ABSTRACT

Despite improvements in survival, cancer remains the leading cause of non-accidental death in children and adolescents, who risk receiving high-intensity end-of-life (HI-EOL) care.

Objective To analyse treatments for relapses (particularly in the last weeks of life), assess their impact on the EOL, identify patients most likely to receive HI-EOL care and examine whether palliative care services can contain the intensity of EOL care.

Methods This retrospective study involved patients treated at the paediatric oncology unit of the Istituto Nazionale Tumori in Milan who died between 2018 and 2020. The primary outcome was HI-EOL care, defined as: ≥1 session of intravenous chemotherapy <14 days before death; ≥1 hospitalisation in intensive care in the last 30 days of life and ≥1 emergency room admission in the last 30 days of life.

Results The study concerned 68 patients, and 17 had HI-EOL care. Patients given specific in-hospital treatments in the last 14 days of their life more frequently died in hospital. Those given aggressive EOL care were less likely to die at home or in the hospice. Patients with central nervous system (CNS) tumours were more likely to have treatments requiring hospitalisation, and to receive HI-EOL care.

Conclusion These results underscore the importance of considering specific treatments at the EOL with caution. Treatments should be administered at home whenever possible. The early activation of palliative care, especially for fragile and complicated patients like those with CNS cancers, could help families cope with the many problems they face.

Key messages

What was already known?

- ▶ Children with cancer experience a heavy burden of symptoms at the end of life (EOL).
- ▶ Patients who receive high-intensity EOL (HI-EOL) care are more likely to die in acute care wards.

What are the new findings?

- ▶ Patients with central nervous system tumours receive HI-EOL care more often than those with other tumours.
- ▶ Patients given aggressive EOL care were less likely to die at home or in the hospice.

What is their significance?

- ▶ The pros and cons of palliative treatment must be carefully weighed, especially in patients with brain tumours.

INTRODUCTION

Although the outcome for children and adolescents with cancer has improved significantly in the last decade, between 2000 and 2008, there were a mean 244 cancer-related deaths a year involving patients under 20 years old in Italy, corresponding to an annual rate of 3.5 per 100 000.¹

Even with advances in treatment and improved survival rates, more than one in four children with central nervous system (CNS) tumours will succumb to their disease.² Children dying from CNS tumours have unique end-of-life (EOL) symptoms, including communication difficulties, dysphagia impairing the

administration of medication, limb paralysis, headache, seizures and cognitive and behavioural changes.³

The use of cancer-directed therapies even when there is no realistic chance of cure is becoming increasingly common, mainly due to patients' accrual into early-phase drug trials. Many parents report afterwards, however, that their children suffered as a result of their agreeing to such treatments, and they would advise other families against doing so.³

Several studies have documented that many children with cancer experience a heavy burden of symptoms at the EOL, due partly to the high-intensity medical care they receive.^{4–7}

Oncologists are sometimes reluctant to activate early palliative care, partly because of their own emotional involvement and awareness of the generally good prognosis of paediatric patients with cancer, and partly because they fear depriving parents of their last hopes.⁸ Advances in cancer treatments have also led to rising numbers of phase I trials postponing the parents' and oncologists' acceptance of a patient's incurability. In some cases, a refusal to accept a poor or uncertain prognosis (when it is difficult to estimate a patient's life expectancy) prompts oncologists to propose oncological treatments—even for palliative purposes—that can result in an excessive hospitalisation of patients near the end of their life.

Much importance has been attributed to the early activation of palliative care also to limit HI-EOL treatment.^{6–9} The availability of palliative care services depends on a patient's area of residence, as it varies widely in different parts of Italy, and some areas lack sufficient resources to provide simultaneous care. In the Milan area, the service has been delivered by a non-profit association under a partnership with doctors specialising in paediatric palliative care (PPC) since 2015.¹⁰ Patients who live elsewhere may be able to access the palliative care available for adults, which is adapted to paediatric patients (where possible) by an ad hoc team.

Aim

We analysed a cohort of patients treated at a paediatric oncology ward, focusing on: (1) treatments they received after a first relapse and in the last weeks of life (type and place of administration) and (2) the impact these treatments may have had on the EOL. Secondary objectives were to ascertain which types of patient were most likely to receive HI-EOL care, and whether activating palliative care service would have affected its intensity.

METHODS

Patients treated at the paediatric oncology unit of IRCCS Istituto Nazionale dei Tumori (Milan, Italy) for a solid cancer and who died between January 2018 and January 2020 were all retrieved and analysed from the department's database. This is a retrospective

chart review. We excluded patients only coming to our hospital to be enrolled in phase I/II trials with new drugs because they were only followed by our team for short periods of time, and decisions regarding their subsequent treatments and when to refer them to palliative care were not shared with us. All other patients treated in the years 2018–2020 were retrieved and analysed.

There are some adult patients in the sample either because they had been diagnosed with cancers of childhood and were consequently treated at our department, or because their disease had first been diagnosed in paediatric age and then relapsed in adulthood. The primary outcome was HI-EOL care, defined as the experience of at least once of the following: (1) ≥ 1 session of in-hospital intravenous chemotherapy or radiotherapy < 14 days before death; (2) ≥ 1 hospitalisation in an intensive care unit (ICU) in the last 30 days of life and (3) ≥ 1 emergency room admission in the last 30 days of life. As there are no defined paediatric criteria of HI-EOL, we used indicators developed from^{7–11} previous population-based research^{4–9–12–13} on children and adults. We added as a further indicator the administration of radiotherapy < 14 days before death as about a half of patients were patients with CNS tumours and this treatment often requires a patient's admission to hospital—especially for patients undergoing reirradiation.

As a whole, we analysed the treatments proposed after a first relapse (chemotherapy or radiotherapy, surgery), the timing and modality of specialised palliative care team involvement, the place of death, emergency room and ICU admissions during the last month of life, and the time elapsing between the last specific treatment and death. Palliative care involvement is usually noted in the medical chart. Preschool age was defined as up to 6 years old. Teenager and young adults were patients > 15 years old. The χ^2 test was used to compare different groups. Significance was set at $p < 0.05$.

RESULTS

Overall 90 patients died during the study. Twenty-two of the 90 patients were excluded from the analysis because they came to our centre only to take part in an early-phase drugs trial. Mean age at diagnosis was 9 years (1–33), at death 13 (2–35). Twenty-nine of 68 patients were female. After their first relapse the median number of chemotherapy lines administered was 1 (range 0–7), and for radiotherapy (for primary tumours or recurrences), it was also 1 (0–6). The patients surviving the longest were those with sarcoma, who were also the patients receiving the largest number of treatment lines (see [table 1](#)). All patient died for disease progression.

Forty-three of 68 patients lived in Lombardy region (26 of them in and around the city of Milan, where our hospital is located), and 25/68 moved from other

Table 1 Characteristics of cohort (n=68): diagnosis, treatment and site of death, lines of therapy according to diagnosis after relapse

Cancer type	Patients, N	Patients %	PCT	Place of death		CT lines Range (0–7)	RT lines Range (0–6)	S Range (0–5)	Months from diagnosis to relapse	Months from relapse to death
				Home/hospice	Other	Mean/median	Mean/median	Mean/median	Mean/median	Mean/median
CNS	35	51	26	22	13	1/1	0.8/1	0.3/0.8	11/9	11/6
Sarcoma	23	34	19	17	6	2/2	0.7/0	0.4/0	16/12	13/5
OS 6, Ewing 6, STS 11										
NBL	6	9	6	5	1	3.1/2.5	0.8/1	0.1/0	34/16.5	17/17
Other	4	6	4	3	1	4/3.5	0.2/0	0.2/0	9.2/7	18/14.5

CNS, central nervous system; NBL, neuroblastoma; OS, osteosarcoma; PCT, palliative care team; S, surgery; STS, soft tissue sarcoma.

Italian regions. Thirty-one of the 68 patients died at home, 16 in a hospice, 9 in our paediatric oncology ward, 11 in other general hospital wards and 2 in ICUs outside Lombardy. The probability of dying at home was significantly associated with the patient's family living not in Lombardy, but in Milan or its hinterland ($p=0.0047$). Patients with CNS tumours died more frequently in hospital (65% vs 45%), though the difference was not statistically significant. Six of the nine patients who died in our ward had CNS tumours (see table 2).

For 62/68 patients, the duration of the chemotherapies and radiotherapies administered was known, while for six patients on oral treatments the time elapsing between stopping their therapy and their death was not recorded. For the former 62 patients, the median time elapsing between the last dose of chemotherapy (either per os or intravenous) and death was 27 days. In the last 2 weeks of life, 21/62 patients (33%) received treatments, which required hospitalisation in 9 cases (14.5%), 7 patients with CNS tumours and 2 with sarcomas. These treatments involved radiotherapy and intravenous chemotherapy in five and four patients, respectively. Patients given specific treatments in hospital in the last 14 days of their life were

more likely to die in the paediatric oncology ward ($p=0.0001$).

When we examined which patients received HI-EOL care, data were available for 65 of the 68 patients, and 17 of them (26%) met at least one of the three criteria to define HI-EOL. Seven admission to emergency department in the last month of life (10%); 5 admission to ICU in the last month of life (7%) and 10 patient (14%) received treatment in hospital last 14 days (intravenous chemotherapy or radiotherapy).

A palliative care programme had been in place for 55/68 patients (80%) (ever since their diagnosis in three cases). Twenty-three out of 55 patients were in the care of a PPC team, and is known the exactly date of involvement of the service, as described in another paper.¹⁰ Other patients received palliative care delivered by teams for adults, which was adapted case by case. Twenty-one of 23 patients in the care of a paediatric palliative team had more than 1 month between first consultation and death.

Patients on a palliative care programme were less likely to receive HI-EOL care ($p=0.0001$).

Patients with CNS tumours ($n=32$) were more likely to receive treatments that required hospitalisation during the last 14 days of their life, though this finding

Table 2 HI-EOL care and site of death

		Place of death						P value	
		Home	Hospice	POU	Other hospital	Home+hospice	Hospital		
Diagnosis									
CNS=35		14	8	6	7	22	13	ns	
Other tumours=33		17	8	3	5	25	8		
HI-EOL (data on 65 points)									
Yes=17		2	4	5	6	6	11	0.0009	
No=48		27	11	4	6	38	10		
Un=3									
Treatment in hospital last 14 days (data on 68 points)	Death in oncology ward								
Yes=9	5 (other=4)	P=0.0001	1	2	6	0	4	5	ns
No=59	4 (other=55)		30	13	4	12	43	16	

CNS, central nervous system; HI-EOL, high-intensity end of life; ns, not significant; POU, paediatric oncology unit; un, unknown.

was not statistically significant ($p=0.06$). Patients with CNS tumours significantly received HI-EOL care more often than those with other solid tumours ($p=0.0188$).

Patients receiving aggressive EOL care ($n=17$) more often died in ordinary hospital wards than at home or in a hospice, and this difference was statistically significant ($p=0.0009$).

When we grouped our series by age at time of death, first distinguishing between preschool-aged children ($n=16$) and older patients ($n=52$), we found that 10/16 patients <6 years old (60%) died at home, as opposed to 21/52 (40%) in the older group ($p=0.36$). When these two age groups were compared in terms of deaths in the hospice, only 1/16 younger patients (6%) died in the hospice, as opposed to 15/52 older patients (28%) ($p=0.12$). When we grouped and compared the patients by age >15 as opposed to <15 years, no significant differences emerged regarding the place of death.

DISCUSSION

EOL management in paediatric oncology always confronts doctors with complex situations because every family, and every single patient, depending on their age and type of cancer, have their own particular features.

This is a mono-institutional study involving 68 patients which shows that 26% of patients receive HI-EOL care during the last 30 days of life. This is the first Italian study regarding the intensity of EOL care in paediatric patients with solid cancer.

Approximately 40 patients treated at our centre die each year.^{10 14} Patients with CNS tumours and sarcomas made up the majority of our series (85%). Patients with CNS tumours are complex cases due to the multiple impairments^{15 16} their disease may cause. Their symptoms can be extremely disabling and difficult for families to handle, for example, swallowing difficulties, communication problems, paralysis with a consequent need for aids like wheelchairs, nasogastric tubes or gastrostomy. These patients also often have complications like hydrocephalus that demand intervention at specialised centres (neurosurgery departments).

The probability of dying at home was significantly associated with the patient's family living in Milan or its hinterland and this is for the presence of a partnership with a paediatric PPC team.¹⁰ Access to palliative care in Lombardy is really different: there are some area well served, some teams, although dedicated to adults, are able to customised their services on paediatric patients. In other area, there is no availability for children.

Drawing a comparison with our previous data,¹⁴ we confirmed a trend towards fewer paediatric patients dying in hospital wards for acute patients (this applied to 34% of a series studied in 2006, and to 16% of the present one) and an increase in deaths in dedicated

structures (8.5% vs 23.5%). The past decade has seen a general tendency to optimise supportive care throughout the course of a disease, including concurrent palliative care services.¹⁰

Comparing the place of death for our patients with other published case series proved quite difficult. Other countries have different healthcare systems, and the availability of territorial palliative care varies, not only within a given country, but even within the same region.¹⁷ That said a recent paper shows that in Ile de France (IDF) the hospital was the most frequent place of death (75% of patients).¹⁷ This proportion has remained stable since 2002 in IDF.¹⁸ Conversely, in the Lyon area, the rate of home death is higher (65%) in relation to a very dedicated and mobile PPC team, a single tertiary centre and a lower population density.^{19 20} In England, hospitals and home were the main EOL setting for children and young adult. The home death rate (~40%) barely changed in the past two decades, and deaths in hospital remained the most common but slightly shifted towards hospices.²¹ In USA, a paper of St.Jude Hospital reported home death in 53%, hospital death in 38% (43% in ICU) and hospice 3.4%.²²

There may also be cultural factors that have a bearing on EOL management choices. There are no recent published data regarding the place of death on the entire Italian territory. Data of 2006–2007 describe 40% of children's suffering from malignant neoplastic diseases die at home: the figure is 60% for southern Italy and 10%–15% in the north; patients in southern Italy often stay at home because of shortcomings at the local hospital or hospice.^{23–25}

Patients who receive aggressive EOL care are more likely to die in acute care wards (or paediatric oncology wards, or paediatric wards closer to home, or ICUs), possibly because of the adverse effects of treatments.^{12 13} The patients most likely to receive HI-EOL care are understandably those with CNS cancer, as their management is extremely complex from early on in the course of their disease, largely for the reasons mentioned above. Another reason lies in the benefits of radiotherapy for palliation for CNS tumours^{26–28} which can only be delivered in hospital (patients frequently need to be admitted if they need reirradiation on the CNS). Suitability of reirradiation, especially in DIPG, should be discussed in a multidisciplinary setting. Reirradiation should be delivered with attention to minimising the risks of toxicity, harm and decreased quality of life in a child's final months.²⁸

Although our study did not report the same primary outcome as more recent studies on paediatric patients and HI-EOL care,^{7 8} we can compare some individual measures of HI-EOL care.

We noted that the proportions of patients in the Ontario series⁸ given intravenous chemotherapy or radiotherapy during the last 2 weeks of life was very similar, while the percentage of cases receiving HI

EOL care as a whole was lower in our series. The latter difference may relate to different, HI EOL criteria, ways in which palliative care is delivered, and health care systems are organised. Our study also concerned a much shorter time interval and was more recent (2018–2020, as opposed to 2000–2012 for the Ontario series).

In the French study,⁷ HI-EOL care was provided more frequently (for 50% of patients vs 26% in our case), but their series only considered patients who died in hospital. It also included patients with leukaemias, and we know that they most frequently die in hospital due either to treatment-related complications or to the less predictable disease trajectories, compared with patients with solid tumours.^{29 30} Revon-Rivière *et al* similarly reported that patients with CNS cancers, together with patients with haematological tumours, were more likely to receive more aggressive EOL treatments.⁷

An extremely different finding that emerged between our patient series and the aforementioned cohorts concerns patients' access to intensive care in the last month of their lives. In our sample, 7% of patients went into intensive care, while in the Canadian and French samples the proportions were 21% and 34%, respectively. This is probably due, once again, to the presence of patients with haematological malignancies in other series, and perhaps to how^{7 8} health care systems are organised.

Compared with our earlier report,¹⁴ it is worth noting that both the number of deaths at home and the proportion of patients given active palliative care had increased over time. As mentioned above, our previous data regarding the concurrent provision of palliative care during the course of a disease showed that patients given active palliative care from early on were at lower risk of experiencing HI-EOL care.¹⁰ Other groups have also reported similar findings.³¹ Research has shown that most parents and clinicians prefer a paediatric patient's EOL care and death to be managed at home,^{32 33} and this is more likely to happen when a palliative care team is involved.³⁴ That said, families are all different, each with their own problems and needs, and home may not always be the ideal place for a terminal patient. Place of residence can also strongly affect the therapeutic strategies adopted and the EOL care available, partly because access to palliative care is by no means homogeneous in Italy.^{23 24}

Patients with cancer sometimes receive treatments up until their death. This may be at the request of the patients themselves or their families, or because their oncologists struggle with the idea of recommending no further treatment to avoid depriving parents of their last hopes.³⁵ Such requests for, or offers of further treatments can sometimes be a source of conflict with palliative care teams, who may judge it better to give the family a clear message regarding their child's prognosis and help them to come to terms with it. On the

other hand, oncological treatments that can be administered at home, without any excessive toxicity or the need for hospitalisation, may help to sustain a family's hopes³⁶ without interfering with the daily activities of the patients and their families.

There is also the matter of the phase I/II trials that some centres (like ours) are accredited to conduct, and a patient's involvement necessarily entails frequent visits to the hospital. Participation in phase I trials does not seem to affect the characteristics of EOL care for paediatric oncology patients,³⁷ but this is only true if palliative care consultations are a routine part of the process for enrolling patients in phase I trials.³⁸

Another issue to consider is the risk of concentrating too much on treatments, or on managing organic symptoms, and not enough on a patient's emotional–existential and spiritual well-being. Even on the subject of planning for the EOL, the more or less explicit wishes of the child/adolescent, and a 'possible heritage' may risk going overlooked. Research has shown that having a proper conversation regarding the aspects involved in the EOL helps families to prepare for the time of death, and even to cope better with their bereavement.³⁹

Limitations: Several limitations of this study should be considered: the sample size is small, as it is a mono-institutional work, so it does not reflect the real situation in our country. For the statistical analysis, we have a lack of a multivariate analysis. We did not capture the preference of the families and the patients about the preference of dying at home, in paediatric oncology unit or the hospital near home. It is not obvious the preferred place for EOL. We missed some data about EOL, some patients living in the south of Italy were cured in the terminal phase by other hospital and we could not have all data.

CONCLUSIONS

Our results highlight the importance of weighing up the pros and cons of specific treatments and their intensity at the EOL, especially when families and patients have expressed the wish to spend the terminal phase at home, since we found that to prescribe intensive rescue oncological treatment during the EOL period correlates with an higher probability of dying far from home. Whenever possible, the proposed treatments should balance the chances of improving the patient's condition with those of offering the best quality of life by providing the best supportive care.

The early activation of palliative care, especially in such fragile and complicated patients as those with CNS cancers, could help families to cope with the many problems they encounter.

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