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End of life care in adolescents and young adults with cancer: Experience of the adolescent unit of the Institut Gustave Roussy

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ABSTRACT

Background: Cancer is the third leading cause of death in adolescents and young adults (AYA). Little is known, however, about how end-of-life unfolds for those who die of progressive disease. In order to better evaluate the specific needs of these patients, we performed this study providing baseline information about end-of-life care patterns for AYA in our department.

Patients: A standardised form was used to collect data concerning all 45 patients treated for a malignancy in the Paediatric and Adolescent Oncology Department at the Gustave Roussy Institute, and who had died of progressive disease above 13 years of age, over a two-year period.

Results: The main diagnoses were sarcomas and brain tumours. Previous cancer-directed treatment included a median of 3 different chemotherapy regimens, high-dose chemotherapy with haematopoietic stem cell support for 13% and radiotherapy for 40%. One in every four patients had been enrolled in a clinical trial at diagnosis. Median survival was 18 months after the diagnosis and 7 months after the first relapse/progression. During the last week of life, the median number of physical symptoms was 4, mostly pain and dyspnoea. Frequent psychological symptoms were sadness, anxiety, fear and guilt. End-of-life care included transfusions, artificial nutrition, corticosteroids, pain control, sedation but also palliative chemotherapy. The median time spent in hospital during the last month of life was 16 days. Most patients had died in hospital.

Conclusions: The terminally ill adolescent displays notable challenges to care providers and requires a holistic approach with the help of a multidisciplinary team.

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1. Introduction

The prognosis for adolescent and young adults (AYA) with cancer continues to improve, and 87% can expect to be alive 5 years after the diagnosis with huge differences in survival rates according to the diagnosis: lymphomas (84–95%) and sarcomas (48–59%).[1] Despite such progress, the remaining 13% of AYA with cancer die, the majority from progressive disease.[2]

During the last 25 years, the incidence of cancer in this age group has risen while the increase in the cancer survival rates has been significantly lower than in younger or older patients.[3,4]

Palliative medicine and adolescent care are both relatively new disciplines[5] with medical practice in this age group still being based on a combination of clinical experience and adult and paediatric clinical guidelines.[6,7] This may not be appropriate as differences between adults and AYA will inevitably influence many aspects of palliative care.

The aim of this study was to provide broad baseline information about the clinical history and patterns of end-of-life care of AYA treated in the Paediatric and Adolescent Oncology Department at the Institut Gustave Roussy who had died in 2007–2008.

2. Patients and methods

2.1. Design of the study

This retrospective study was conducted in the Paediatric and Adolescent Oncology Department, at the Institut Gustave Roussy in Villejuif, France.

Patients, above 13 years of age, were considered eligible if (a) they had consulted at least once in the Paediatric and Adolescent Oncology Department (b) they had died as a result of a progressive malignancy and (c) death had occurred between 1st January 2007 and 31st December 2008.

2.2. Data collection

Data were collected by one paediatrician (S.C.-G.) on a standardised form (Supplementary Table 1) through a retrospective medical and – when available – a nurse's chart analysis.

We collected data concerning the clinical history of cancer and cancer treatment, patterns of physical symptoms during the last week of life, the care provided during the last month of life, the cause and place of death. Regarding physical and especially refractory symptoms, a paediatrician (S.C.-G.) and a pain and palliative care expert (S.L.) re-examined indications for sedation or alternative symptom control in the medical files. The AYA unit psychologist (G.M.) reviewed her notes concerning interviews during the last month of life and collected psychological symptoms.

3. Results

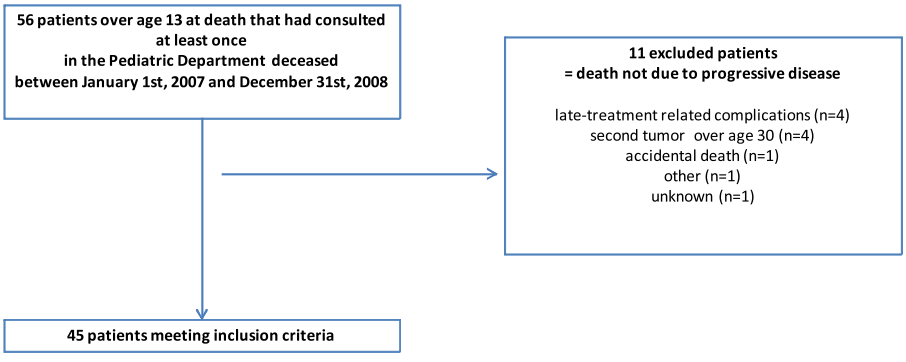
3.1. Patients and cancer-directed treatment

3.1.1. Patient population

Patient selection can be found in detail in Fig. 1. Overall, among the 56 patients who had consulted at least once in the Institute and died between January 2007 and December 2008 above the age of 13, 45 were available for the data analysis: 23 patients had died in 2007, 22 in 2008. Patient characteristics are listed in Table 1.

3.1.2. Cancer-directed treatment history

The place of initial care was the Paediatric and Adolescent Oncology Department for 35 patients (78%). Nine patients



Second tumors (n=4) were a radio-induced meningioma, a radio-induced osteosarcoma, a radio-induced sarcoma, a hepatocellular carcinoma.
Late-treatment complications (n=4) included

- extensive pulmonary infection over fibrotic lung from radiotherapy,
- viral infection with multiple organ dysfunction,
- viral infection in a cardiac graft recipient (anthracycline-induced cardiomyopathy),
- brain surgery post-op (suspicion of radio-induced meningioma)

Other cause of death (n=1) is related to a septic shock in a myasthenic patient in complete remission.

Fig. 1 – Flowchart representing patient selection.

Table 1 – Patient characteristics, initial care, remission achievement and survival.

Patient	
Age at diagnosis, years	
Median (range)	15.9 (5.2–24.2)
Age at death, years	
Median (range)	18.1 (14.2–26.2)
Gender, *n* (%)	
Male	30 (66.7)
Known cancer predisposition, *n* (%)	4 (8.9)
Disease type, *n* (%)	
Sarcomas	19 (42.2)
Brain tumours	16 (35.5)
Leukaemias/lymphomas	3 (6.7)
Other solid tumours	7 (15.6)
Treatment	
Associated care at local hospital, *n* (%)	26 (57.7)
Treatment duration, years	
Median (range)	1.5 (0.1–13.6)
No. of cancer-directed regimens, *n*	
Median (range)	3 (1–11)
No. of chemotherapy drugs, *n*	
Median (range)	7 (0–16)
High-dose chemotherapy as first-line treatment, *n* (%)	6 (13.3)
Radiotherapy as first-line treatment, *n* (%)	18 (40)
Enrolment onto clinical trial for first-line treatment, *n* (%)	11 (24.4)
Enrolment onto phase I–II study for a relapse, *n* (%)	9 (20)
Complete remission after initial treatment	
All patients, *n* (%)	22 (49)
Leukaemias/lymphomas patients, *n* (%)	3 (100)
Sarcoma patients, *n* (%)	12 (63)
Brain tumour patients, *n* (%)	3 (19)
Relapses/survival	
Relapses before fatal relapse/progression	
Median (range)	1 (0–6)
Survival time, months	
Median (range)	18 (1–163)
Survival time from first relapse/progression, months	
Median, range	7 (0–130)

n, number of patients; %, percentage of patients.

had received initial care in another paediatric oncology unit and one in an adult oncology unit.

Data on first-line treatment and on the remission achievement status are presented in Table 1. Data on overall survival are presented in Table 1. Survival after the first relapse/progression was significantly shorter for patients who had never achieved a complete remission or who had developed an early relapse (less than 2 years) as compared to patients who had developed a late relapse ($p = 0.02$) (Fig. 1). Median survival after the diagnosis or the first relapse/progression also varied according to the tumour type: patients with sarcoma had the longest survival after the first relapse or progression (15 months, range 0–39 months) whereas the survival of patients with brain tumours was only 7 months (median, range 0–54 months) after the first relapse/progression.

3.2. *Symptoms*

3.2.1. *Physical symptoms*

During the terminal phase, the median number of physical symptoms reported was 4 per patient (range, 1–7 physical symptoms). The most frequent physical symptoms were pain and dyspnoea (Fig. 2). The tumour type influenced the prevalence of physical symptoms (Fig. 3). Patients with sarcomas experienced pain, dyspnoea and fatigue whereas brain tumour patients experienced paralysis, confusion or coma more frequently. The high prevalence of dyspnoea in patients with sarcoma (63%) was related to various mechanisms such as upper airway obstruction, pulmonary metastases or a compressive abdominal mass.

3.2.2. *Psychological symptoms*

During first-line treatment, 77% of patients had undergone at least one interview with the AYA unit psychologist. Half of them had received a more intense follow-up afterwards, for reasons such as psychiatric issues, troubled social and family life or psychological suffering. During the last month of life, the symptoms reported by the patients to the AYA psychologist were numerous (Fig. 4).

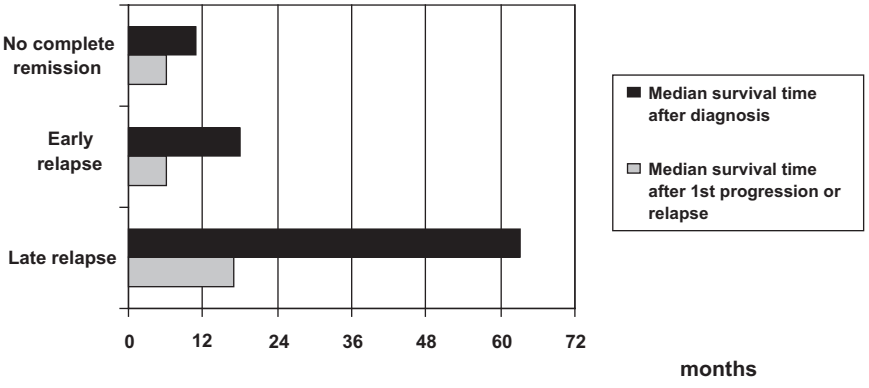


Fig. 2 – Several survival profiles were observed, according to the duration of survival after the diagnosis and after first relapse/progression.

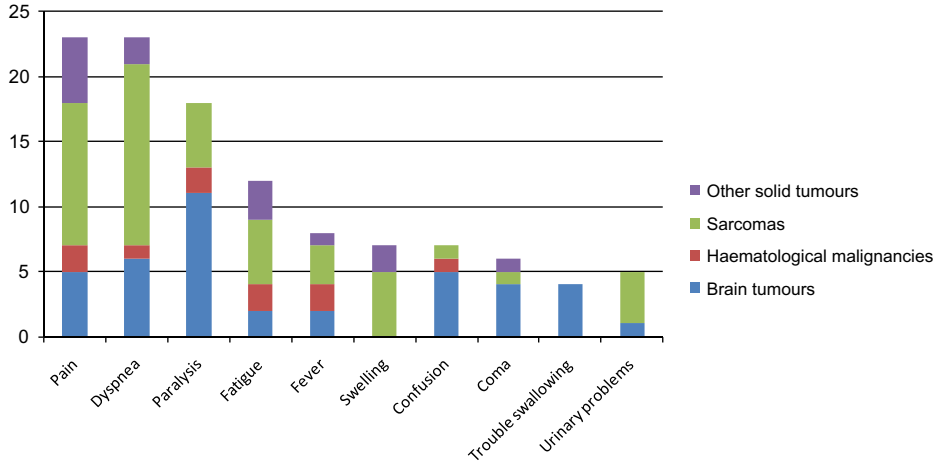


Fig. 3 – Physical symptoms reported during the last week of life, according to diagnosis.

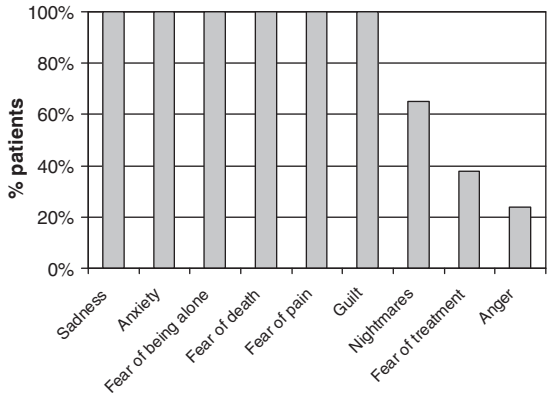


Fig. 4 – Psychological symptoms during the last month of life.

Table 2 – Palliative and terminal care characteristics.

Palliative/terminal care	
Blood products during last month, *n* (%)	12 (31.6)
Supportive care during last week, *n* (%)	
Opioids	32 (84.2)
Corticosteroids	23 (63.8)
Enteral nutrition	8 (22.2)
Parenteral nutrition	4 (11.1)
Refractory symptom control	17 (37.7)
Sedation	6 (13.3)
Place of death, *n* (%)	
IGR – Paediatric Department	20 (44.4)
Local hospital	6 (13.4)
Home	6 (13.4)
Adult palliative care unit	4 (8.8)
IGR – Intensive Care Unit	2 (4.4)
Foreign country	2 (4.4)
Unknown	5 (11.2)

n, number of patients; %, percentage of patients; IGR, Institut gustave Roussy.

3.3. *End-of-life care*

3.3.1. *General data*

Most patients (95%) had been fitted with a central blood line before or during end-of-life care. Eighteen patients (40%) had received palliative chemotherapy during the last month of life. The median time between the last course of chemotherapy and death was 30 days (range, 2–457 days). Local radiotherapy had been delivered to 11 patients mostly for pain and symptoms related to the tumour volume. Supportive care included blood and/or platelet transfusions, parenteral or enteral nutrition, corticosteroids and analgesic drugs including opioids (see Table 2). Expert assessment by a doctor trained in pain management and palliative care had been required for 22 patients during the last month of life.

Among the 35 patients who had met the AYA psychologist during initial care, 29 had continued to attend regular sessions during the palliative phase. The reasons for interrupting follow-up were home-based care, refusal or the family needed to focus on the AYA.

3.3.2. *Pain control*

Thirty-two patients (84%) had required opioids for pain control. The median duration of opioid treatment before death was 39 days (range, 1–226 days). Most patients had been treated with morphine, either orally ($n = 10$) and/or intravenously ($n = 13$). Fentanyl was most commonly used when the transdermal route was chosen ($n = 6$). Non-opioid drugs had been administered to 70% of the patients, mainly as co-analgesics in combination with opioid drugs for neuropathic pain control.

3.3.3. *Refractory symptoms*

Eighteen patients (40%) had required specific care for one or several refractory symptom(s) during the last month of life, mainly for pain uncontrolled by opioids ($n = 6$), dyspnoea ($n = 9$), anxiety ($n = 7$), agitation/restlessness ($n = 1$) and insomnia ($n = 1$). Six patients had experienced more than one symptom.

3.3.4. Sedation

When symptoms had not been controlled despite repeated and careful assessments by skilled experts and the use of all possible treatments (i.e. considered as refractory symptoms), the indication of sedation was discussed by the multidisciplinary team.

Six patients (13%) had received a sedative treatment during the last week of life. The indications for sedation were dyspnoea ($n = 4$), uncontrolled pain ($n = 3$) and bleeding ($n = 1$). Five patients had received intravenous midazolam and 1 patient, intravenous clonazepam as first-line sedative treatment. This first-line sedative treatment had proven ineffective in 4 patients. Those patients had then been switched to gamma-hydroxybutyrate, which was effective. The median time between the initiation of sedation and death was 2 days (range, 0–5 days).

3.3.5. Time spent in hospital during the last month of life, place of death

During the last month of life, patients had been hospitalised over a median time of 16 days (range 0–30 days). This time was significantly shorter for the 6 patients who had died at home versus those who had died in hospital: 7 days (median, range 0–15 days) versus 18 days (median, range 2–30 days) ($p = 0.01$). For the patients who had died in hospital, the final hospitalisation lasted an average of 13 days (range, 1–38 days). Most of the patients had died in the Paediatric and Adolescent Oncology Department (44%). Other places of death are shown in Table 2. There was no difference in the place of death according to the tumour type. Six patients had died at home, in keeping with either the patient's and/or the family's request. Eight other patients who had received home-based care had been hospitalised within a median of two days before death (range, 1–14 days). The reasons for hospitalisation before death were loss or a decreased level of consciousness, acute dyspnoea, uncontrolled pain and extreme fatigue. Four patients had died in a palliative care unit and were all young adults.

4. Discussion

This study provides broad baseline information about the clinical history and patterns of end-of-life care of adolescents and young adults (AYA) treated in a specific AYA unit in a French Paediatric and Adolescents Oncology Department.[8]

There are several important limits to this work: it is retrospective, with data from a single department. We are aware that our collection of symptoms may not be exhaustive and that a lot of statements depend on local arrangements, clinical practice and networks. As expected when considering the survival rates of different tumour types in this age group[9], the main diagnoses in our cohort were brain tumours and sarcomas. The scarcity of haematological malignancies in our cohort is due to the fact that our unit specialises in the management of solid tumours.

In most patients, end-of-life care had continued to be an active period of care and consisted of multiple interventions, including specific anti-tumour therapy. Forty percent had received palliative chemotherapy with different and interconnected goals, mainly relative tumour growth control and pain relief. This is in line with published data concerning 23–43% of adults with incurable cancer who received chemotherapy during the last month of their lives.[10] Up to 20% of patients had been enrolled in phase I or II clinical trials for a relapse. The important role of our department in new drug development had led to the referral of patients from other centres to our institute so that they were able to receive new innovative therapies in the relapse context. In this context, the limits between curative and palliative treatment are not always obvious. Patient and family expectations from these investigational treatments were difficult to assess retrospectively from the medical charts. Serious considerations about the autonomy of the adolescent in the decision-making process are required when conducting such studies.[11] Unfortunately, we could not study this specific point from our clinical charts, but it will require a prospective analysis in the future.

Most of the patients experienced substantial physical and psychological symptoms during the last week of life. Half of the patients had experienced four or more physical symptoms. As expected[12–14], there were differences in reported symptoms according to the tumour types (see Fig. 3). Psychological symptoms were poorly reported in the medical files, even though they had been present in all of the patients, as observed by the AYA psychologist by a review of her notes. To our knowledge, this is the first study to collect psychological symptoms with such an approach in this age group. In other studies, psychological symptoms are retrieved either from medical files[15] or through a questionnaire sent to the parents after the death of their child.[12,13] These studies reported a lower incidence of sadness (17–65%), anxiety (27–35%), guilt (12%) or fears (22–41%) than our data. The high number and prevalence of psychological symptoms collected showed that AYA had been able to share stressful feelings with the AYA psychologist. Systematic evaluation and support from an AYA psychologist appeared to be an important part of the care that could be given at that time of life.

One third of the patients had received artificial nutrition during the last week of life. However, there is no evidence that the use of medically assisted nutrition or hydration at the end of life prolongs survival in adult patients. In the United States, it has become an accepted standard of practice in palliative care settings to avoid the use of medically assisted nutrition and hydration (ANH).[16] This standard is still difficult to apply in a paediatric setting in which families, patients and even some health professionals perceive failure to provide ANH as sometimes equivalent to active starvation.

Almost half of the patients had required an intervention from the palliative care and pain treatment teams in the Institute. Close interaction between the "AYA team" and the palliative care team is therefore essential, and should lead to early interaction or referral, as recently proposed by Wein et al.[7] As pain was the main symptom observed, end-of-life care involved opioid use in the great majority of patients. Another finding of our study was that 13% of patients had required sedation during the last week of life. Midazolam was the drug commonly used for sedation, according to guidelines.[17,18] However, it proved to be inefficient in some patients who had to be switched to gamma-hydroxybutyrate, a natural metabolite of gamma-aminobutyrate that may act as a

neurotransmitter via its own receptors and via the stimulation of GABA-B receptors and regulates sleep.[19] Although there are no published recommendations about its use in the palliative or end-of-life care setting, this medication has been used for years in patients requiring end-of-life sedation in our Department and is often more efficient than midazolam in our everyday clinical experience. Concerning the time spent in hospital and the place of death, we found that most of the admitted patients had spent more than 2 weeks in hospital during their last month of life. Only a few patients had died at home and had spent less time in hospital. These data are at variance both with other published data concerning children[20–22] and with those relative to children under 13 years old treated in the Paediatric and Adolescent Oncology Department at the same period: among those younger patients, 20% had died at home and 38% in the local hospital. These results suggest that home-based or local hospital care may be more problematic for AYA than for younger patients or adults. Still, other French paediatric oncology departments show a different picture. In Lyon, 75% of children receive end-of-life home care thanks to trained and available care givers, with more and more families and patients willing to take this step back home.[20] This is consistent with data concerning adults that shows that approximately two thirds of cancer patients, when asked about the preferred place of death, wish to die in their own homes.[23]

Nevertheless, most patients in our cohort had died in the Paediatric and Adolescent Oncology Department and the great majority among them in the AYA unit. However, as stated above, other approaches offer other advantages for these patients and their families, especially in choosing where end of life should take place. Around Paris, mobile units that deliver paediatric palliative care at home are being developed thanks to the newly launched Paliped network. Still, structures such as paediatric palliative care units, paediatric hospices or respite houses[24–26], do not exist.

Palliative care units are designed for adults and might not be adequate for teenagers since most caregivers are still not trained for the care of terminally ill adolescents and their unique psychological needs.

This large amount of baseline data reflects our local practice in end-of-life care for AYA. These patients display numerous and diverse symptoms that require a well-trained multidisciplinary team. Most of the time, they do not pass away at home although they should be allowed to. We intend to compile an exhaustive and prospective collection of the patient's symptoms and wishes in order to provide a better end-of-life care; guarantee a multidisciplinary approach in the different places where their life may end and improve the role entrusted to the adolescent in the decision-making process.

Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejca.2011.09.008.

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