Journal of Neuro-Oncology (2018) 138:147–153
https://doi.org/10.1007/s11060-018-2781-0

CLINICAL STUDY

End-of-life care of children with diffuse intrinsic pontine glioma

Fyeza Hasan[1] · **Kevin Weingarten**[1,2] · **Adam Rapoport**[2] · **Eric Bouffet**[1] · **Ute Bartels**[1]

Received: 1 August 2017 / Accepted: 28 January 2018 / Published online: 3 February 2018

Abstract
The end-of-life management of children with diffuse intrinsic pontine glioma (DIPG) is challenging. Families cope with debilitating symptoms and make complex decisions regarding their child's care. However, there is little evidence guiding palliative care provision for these children. Our objective was to describe the dying trajectory of children with DIPG, their symptoms, the care they require and the end-of-life decisions made for them. This retrospective cohort study analyzed the end-of-life care of 41 consecutive patients with DIPG who died between January 2001 and June 2010. All patients died of disease progression, experiencing a significant symptom burden prior to death. Despite this, the majority of patient days at the end of life were spent at home. However, 60% of patients were hospitalized at least once in their final 3 months, often close to the time of death. A wide range of healthcare professionals were involved, providing a range of medicinal/non-medicinal interventions. Chemotherapy was given to 30% of patients in their final month. Thirty of 33 families approached (91%) agreed to a "Do not resuscitate" order. A small subset of families opted for intensive treatment towards the end of life including cardiopulmonary resuscitation, intensive care admission and mechanical ventilation. Children with DIPG have complex needs and require intensive multidisciplinary support. This paper describes the end-of-life choices made for these children and discusses how these choices influence our institutional model for palliative care. We believe this approach will be useful to clinicians caring for similar patients.

Keywords Diffuse intrinsic pontine glioma (DIPG) · Pediatric oncology · End-of-life care · Palliative care

Introduction

Children with diffuse intrinsic pontine glioma (DIPG) face a dismal prognosis with a 2-year survival rate under 10% [1–3]. In the months before death, disease progression leads to the development of symptoms that may be debilitating and significantly impact quality of life. The end-of-life management of these children can be complex and challenging both for families and health professionals. It is, therefore, of great importance to develop an evidence base for the provision of high-quality palliative care to this population. However, few studies have attempted to describe the dying trajectory and end-of-life needs of these children.

The aim of this study was to describe: (1) the clinical course of children with DIPG during their last 3 months of life; (2) the symptoms experienced and management strategies employed during this period; (3) the health professionals involved and organization of care; and (4) decision-making regarding end-of-life care.

Patients and methods

A retrospective chart review was performed including consecutive patients with DIPG who died between January 2001 and June 2010 and were treated at a large Canadian Pediatric Oncology Center. Cases were identified using the hospital Neuro-Oncology database which captures all new brain tumor diagnoses. Diagnostic criteria included the classical clinico-radiological findings of DIPG: Short history (under 6 months) of at least two of three neurological abnormalities (ataxia, cranial nerve palsies, long tract signs) and

✉ Fyeza Hasan
fyeza.hasan@sickkids.ca

[1] Paediatric Neuro-Oncology Program, The Hospital for Sick Children, University of Toronto, 555 University Avenue, Toronto, ON M5G1X8, Canada

[2] Paediatric Advanced Care Team, The Hospital for Sick Children, 555 University Avenue, Toronto, ON M5G1X8, Canada

characteristic MRI findings (a T1 hypointense, T2 hyperintense tumour centered within and diffusely infiltrating at least 50% of the pons). Biopsies were undertaken in case of any atypical findings [4]. All MRIs were reviewed at multidisciplinary team rounds upon original diagnosis. Hence no further radiological review was deemed necessary for this study. Eligible patients were diagnosed under the age of 18 and treated and followed by the institution. Patients were excluded if their end-of-life care (last 3 months) was coordinated by an outside hospital.

Demographic and clinical information was extracted from each patient chart relating to the clinical course and treatment from the time of diagnosis. Further detailed data were obtained from each chart focusing on the final 3 months of life, including symptoms experienced, interventions provided (nutritional, communication and mobility aids, ventriculoperitoneal shunts and ventilation), care provision (location of end-of-life care and health professionals involved) and end-of-life choices (place of death, use of cardiopulmonary resuscitation (CPR), "Do Not Resuscitate" (DNR) orders and autopsies). Medication use was documented for the last month of life.

This study was approved by the institutional Research Ethics Board.

Statistics

Simple descriptive statistics (medians, percentages, ranges, interquartile ranges) were used to summarize the data.

Results

Patient population

During the study period, 48 children died of DIPG. Of these, 6 were managed by outside centers during their final 3 months and 1 was lost to follow-up. Information is presented on the remaining 41 children (19 male, 22 female).

Clinical course and cancer-directed treatment

The median age at diagnosis was 6.8 years (range 0–15.5 years). At diagnosis 38 (92%) of the 41 patients received cancer-directed treatment (90% radiation, 78% chemotherapy, 12% biopsy, 5% limited resection). One of these 38 patients was deemed too young to receive radiation and received chemotherapy alone. Limited resections were performed in 2 patients with atypical radiological findings due to exophytic components and were consistent with the diagnosis of DIPG. No biopsy targeted therapeutic protocol was open at the institution during the time period studied.

The remaining 3 (7%) patients were infants and did not receive disease-directed treatment due to a combination of age and clinical status at presentation. Two of these 3 patients were diagnosed as neonates and died within their first few weeks of life.

At progression, 19 (46%) of 41 patients received cancer-directed treatment. This was always chemotherapy/targeted treatment. Regimens used included oral drugs (Zarnestra, Temozolomide with/without Celebrex) and intravenous Nimotuzumab. A median of 1 line of treatment was given per patient after progression (range 1–3) and 45% of these treatment courses were given in the context of a phase I or II trial at our institution. During the study period, re-irradiation was not yet offered. In the last month before death, 30% of patients received chemotherapy/targeted agents.

All patients died of disease progression. Fifteen percent of patients were also suspected to have aspiration pneumonia at the time of death (Fig. 1).

Location of care in the final 3 months

The majority of patients remained at home for most of their final 3 months of life. One newborn patient died before discharge from hospital. Of the remaining 40 patients, 24 (60%) were admitted to hospital at least once in their final 3 months. The median number of admissions per patient

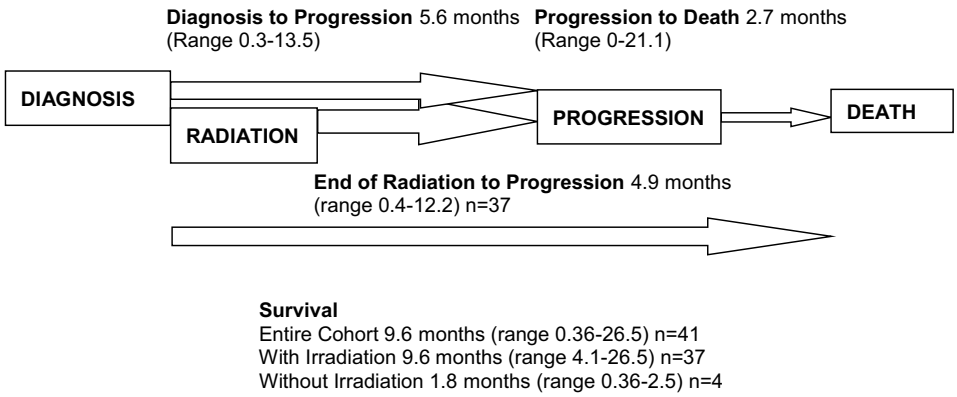

Fig. 1 Timeline of the clinical course indicating median survival and other important time intervals. All times shown are medians. The number of patients is indicated where it is less than 41

was 1 (range 0–2), and the median length per hospital stay was 4 days (range 1–36 days). Children spent 254 of a possible 3480 days (7%) as inpatients during their last 3 months (Fig. 2). Two-thirds of all admissions occurred in the final month of life. Twenty-one percent of admissions involved some time spent on an intensive care unit (ICU). Admission usually occurred for management of symptoms, most commonly pain or respiratory compromise, often following acute deterioration.

Care providers

Palliative care was provided by the Neuro-Oncology service. Fifty-nine percent of families received additional support from an inpatient or outpatient palliative care specialist. In the first half of the study, 29% of patients were followed by a palliative care specialist, increasing to 92% in the second half. During the study period, the palliative care team at our institution consisted of 1–2 full-time specialist nurses and a single part-time specialist physician.

Each patient had a Primary Physician directing their end-of-life care. Physicians with varying backgrounds took on this role: Pediatric Oncologists (39%); Community Pediatricians/Palliative Care Physicians (29%, 15%); Family Doctors (12%); and Intensivists for children on ICUs (5%).

Care providers from a range of multidisciplinary teams provided additional support (Table 1). A median of seven different multidisciplinary teams was involved per child (range 0–9).

Contact generally occurred on an as needed basis.

Table 1 Multidisciplinary teams involved in the final 3 months of life

Multidisciplinary teams	Number (%) of patients (n = 40)
Social work	37 (93)
Community nursing	35 (88)
Occupational therapy	24 (60)
Dietetics	16 (40)
Physiotherapy	16 (40)
Speech therapy	11 (28)
Pastoral care	9 (23)
Child life	5 (13)
Psychiatry/psychology	4 (10)
Music/art therapy	4 (10)

Data available for 40 patients

Symptoms

All patients experienced symptoms in their final 3 months, with a median of seven symptoms documented per patient (range 1–13) (Fig. 3).

Interventions and medications

A range of interventions were provided for patients in their final 3 months (Table 2). No child had a gastrostomy tube inserted in their last 3 months, but 3 patients (7%) had one placed prior to this time (1 at diagnosis, 2 after progression).

A small subset of patients received intensive interventions following disease progression.

A total of seven (17%) patients received some form of mechanical ventilation in their last 3 months of life (excluding elective anesthesia). This includes the two neonates who required ventilation whilst diagnosis was

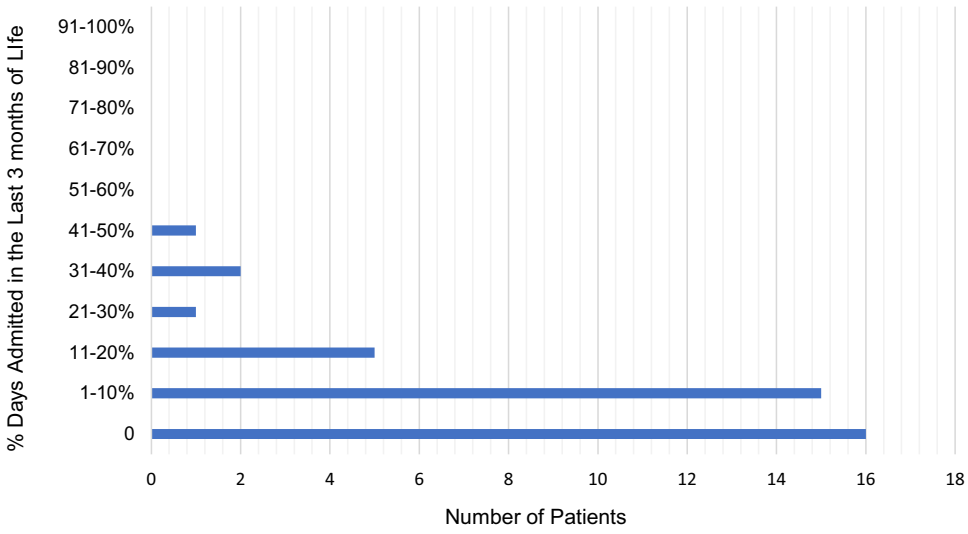

Fig. 2 Percentage days of hospital admission per patient in the last 3 months of life

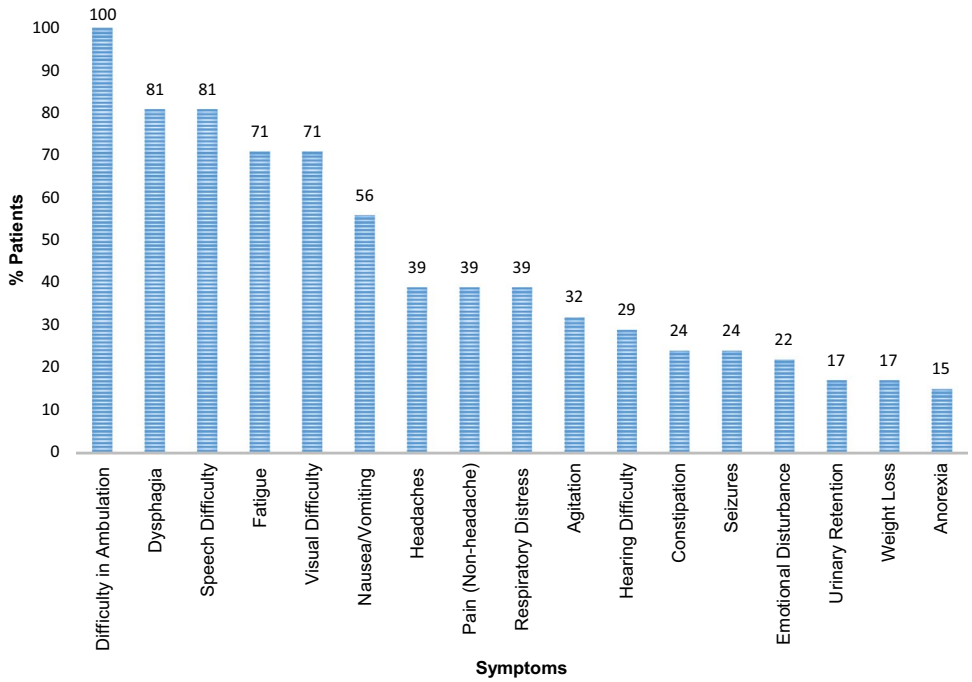

Fig. 3 Symptoms documented in the last 3 months of life agitation is defined as irritability, aggression or confusion. Emotional disturbance is defined as anxiety, depression and other affective symptoms

established. One neonate was weaned from the ventilator, and discharged home breathing independently. Ventilation was withdrawn from the second, who died shortly afterwards. Of the remaining patients, 3 received a short period of mechanical ventilation in their final 3 months (1 invasive; 1 non-invasive; and 1 both). These patients all experienced respiratory compromise in their final days, and ventilation commenced during CPR. One of these patients required only brief ventilatory support which was successfully weaned; the two other patients died following planned discontinuation of mechanical ventilation. Two additional patients received long-term mechanical ventilation via tracheostomy at parental request, which commenced prior to their final 3 months; they both died at home.

Ventriculoperitoneal shunts were placed for 2 (5%) of the patients in their last 3 months, although a further 3 (7%) had shunts placed before that time. Portacaths were placed in 4 (10%) of the patients in their final 3 months to facilitate chemotherapy administration.

A medication history was available for 39 patients (Table 2). A median of 5 drugs was prescribed per patient (range 0–18). Only 49% of patients received opioid analgesia. One patient received palliative sedation with continuous Morphine and Midazolam for end-of-life pain and agitation. Oral Dexamethasone was used to aid pain and symptom management for 62% of patients. Side-effects were noted in 54% of those treated, and 33% became cushingoid. Detailed information on dosing and length of dexamethasone courses was not fully available.

End-of-life choices and decision-making

The last cancer-directed treatment (radiation, chemotherapy or surgery) was administered a median of 54 days (IQR: 23–179 days) before death. However, 12 (30%) patients received chemotherapy in their last month (20% oral, 10% IV) (Table 2).

Ultimately, 23 (56%) children died at home. The remaining 18 (44%) died in hospital, with 12 deaths on an inpatient ward, 3 in the emergency room (ER) and 2 in an ICU (exact location undocumented for 1 death). In the first half of the study period, 39% of patients died in hospital, compared to 50% for the second half. No child died in a hospice, reflecting a historic absence of local paediatric hospice beds.

A DNR discussion was documented in 80% of patient charts. Thirty of 33 families approached (91%) agreed to a DNR order, written a median of 28 (IQR: 11–68) days before death. However, 4 of these 30 patients received CPR in their final month. All 4 presented to hospital with respiratory compromise. One of these children had a DNR in place at this time, but their parents called emergency services when their child became unwell, and did not provide the paramedics with the DNR. This patient stabilised briefly before death and didn't receive mechanical ventilation. The other 3 patients only had their DNR orders established after initial resuscitation, and were all mechanically ventilated, as described before. None of the 11 (29%) patients without a DNR order received CPR in their final month.

A further 2 patients presented to hospital in extremis in their final hours, but were not resuscitated, dying in the ER

Table 2 Interventions provided in the last 3 months of life and medications prescribed in the last 1 month

	Number (%) of patients
Interventions	
Nasogastric tube	20 (49%)
Wheelchair[a]	23 (61%)
Communication aid[a]	11 (32%)
Portacath	4 (10%)
Invasive ventilation[b]	4 (10%)
Non-invasive ventilation[c]	2 (5%)
Ventriculoperitoneal shunt	2 (5%)
Total parenteral nutrition	1 (2%)
Medications[d]	
Steroids	24 (62%)
Opioid analgesia	19 (49%)
Antiemetics	17 (44%)
Laxatives	11 (28%)
Anxiolytics	8 (20%)
Oral chemotherapy	8 (20%)
Anticonvulsants (for treatment or prevention of seizures)	7 (18%)
Non-opioid analgesia	7 (18%)
Antisecretory drugs	6 (15%)
Antispasmodics	6 (15%)
Complementary therapies[e]	6 (15%)
Intravenous chemotherapy	4 (10%)
Osmotic diuretic (for raised intracranial pressure)	2 (5%)
Palliative sedation	1 (3%)

[a]Wheelchair and communication aid use was documented for 38 patients diagnosed after infancy

[b,c]Invasive ventilation refers to ventilation delivered via endotracheal tube, whilst non-invasive ventilation refers to BiPAP (Bilevel Positive Airway Pressure)

[d]Medication data is available for 39 patients

[e]Complementary therapies include homeopathic drugs, Chinese herbal medications and vitamins

shortly afterwards. One had a DNR written in the ER and the second had no DNR order.

Twenty one (51%) of the charts documented a conversation regarding autopsy. Ultimately, autopsies were performed on 12 (29%) of the cohort.

Discussion

Although end-of-life care in DIPG is complex and challenging, there is a paucity of literature guiding the palliative management of these patients. This study provides one of the first detailed descriptions of palliative care requirements in DIPG. We corroborate previous data demonstrating the devastating profile of symptoms patients experience and the intensive interventions and multidisciplinary support required to manage them [5]. We go beyond previous literature in describing the end-of-life choices made on behalf of these patients, discussing below how these choices influence our institutional model of care.

Despite the universally fatal diagnosis, half of our families requested cancer-directed treatment at disease progression. Re-radiation was introduced as a treatment modality for DIPG at our institution after 2010. Hence, no child received re-irradiation and treatment at progression often involved enrolment in early phase studies at our institution. Consistent with previous literature, many families pursued treatment until the end, and one-third of patients received chemotherapy/targeted therapy in their final month [6–10]. These treatments were generally well tolerated oral or infrequently administered IV medications. However, none of these agents were subsequently shown to be effective in DIPG [11]. This may be of concern as previous studies associate cancer directed treatment at the end of life with child suffering and parental regret [6, 7]. Furthermore, clinicians may feel ethically challenged by requests to provide treatments with uncertain efficacy in this context. In prescribing chemotherapy at the end of life, we are clear with families that the intent is to meet specific palliative goals such as improving quality of life or decreasing symptoms. Where chemotherapy fails to achieve those goals or causes more harm than good, we recommend discontinuation. Rarely, chemotherapy is continued for purely psychosocial reasons, but only in the absence of harm to the child. These situations are always challenging, but goal directed, shared decision-making mitigates many concerns.

Two-thirds of our patients had a DNR at the time of death. Many clinicians believe DNR discussions should occur early in the course of a life-limiting illness, ideally at a time of stability, with clinicians who know the child best. Indeed, the majority of those families who were offered a DNR accepted it, and it may be that they found this discussion helpful within a broader conversation that allowed their wishes to be respected in a large, complex healthcare system. It is, then, perhaps, surprising, that one-third of patients did not have a DNR and that, consistent with the literature, orders were often instituted late in the disease course [12]. A lack of a DNR in end-stage cancer may concern clinicians who fear that CPR may lead to child suffering, parental regret and provider moral distress. We were unable to elucidate barriers to DNRs but note that few patients received CPR, and none without a DNR received resuscitation in their final moments. This leads us to ask whether the existence of a DNR is often unrelated to the course of end-of-life events. In our experience, few of the families who are unable to agree to a DNR actually request resuscitation when the time comes. As such, although DNRs can be important elements

of end-of-life care, an over-emphasis on 'getting the DNR' may be unnecessary. Whilst it is theoretically possible (if legally complex) to institute a DNR against parental wishes in Canada, we find that it is rarely necessary or helpful to do so.

Families of children with cancer value the opportunity to plan the place of death, with many preferring death at home [13, 14]. We demonstrate that despite complex needs, intensive support can allow many children with DIPG to be cared for and die at home. Furthermore, round-the-clock oncology and palliative care support can allow community-based physicians without specialist expertise to provide day-to-day care. However, we note that a significant proportion of children were admitted to hospital in their final months. Although we did not examine qualitative data, our experience suggests that some families prefer the supportive environment of hospital. Alternatively, increased community-based support may prevent some admissions.

Consistent with the desire for treatment until the end, a small subset of patients was admitted to an ICU towards the end of life, with one death ultimately occurring in intensive care. Several recent reviews demonstrate an increasing proportion of cancer deaths occurring in the ICU over time, despite increasing palliative care awareness and resource availability [15, 16]. Reasons for this are unclear and likely multifactorial, but it may be that intensive care at the end of life is now viewed as "normal" in our society.

We aim to avoid prescribing steroids wherever possible in progressive brain cancer. Doses are kept low and weaned as quickly as possible. Although steroids alleviate symptoms quickly and effectively, increasing doses are needed over time, with increasing side effects. Nonetheless, similar to a UK cohort, a significant proportion of our patients received dexamethasone, in our case, often initiated outside the Neuro-Oncology team [5]. There have been recent calls for the development of evidence-based guidelines for steroid prescription in DIPG [5, 17]. While we concur with this recommendation, we note a lack of research exploring parental perceptions of the benefits and harms of steroids which guidelines must take into account. In our experience, some families are extremely reluctant to wean steroids, whereas others acknowledge initial benefits, but later regret the side effects [18].

Institutional model of care

Our approach to palliative care arose from an awareness of the choices made by the families affected. Our multidisciplinary team provides a parallel model of care, with concurrent palliative and tumor-directed therapy. We introduce palliative care services as early as possible in the disease course, with early and frequently repeated exploration of individual families' goals and preferences, including preferences for resuscitation and location of care. However, a key aspect of our approach is child- and family-centered care, which acknowledges that whilst guidelines exist, there is no 'one-size-fits-all' approach to any disease, least of all this complex condition. With numerous clinicians caring for each patient, meticulous communication is required to ensure that care is well coordinated. It is also vital to identify a most responsible team for each patient to act as the default conduit for communicating with the family.

Future developments

The landscape of tumour-focused management in DIPG is changing. The increasing use of diagnostic modalities including biopsies, warm autopsies and molecular profiling, and therapeutic innovations like convection-enhanced treatment delivery may influence the disease experience and palliative care needs in ways that are currently unclear.

Limitations

This study has several limitations. It relies on the accuracy of clinical charting. Symptoms were not documented using validated scoring systems, and may underestimate the true symptom burden. Similarly, we had limited ability to judge the impact of interventions. Another criticism may be that this is a single center study, but we believe our practice reflects care provided in other high-income countries. Lastly, the voices of families and clinicians are missing in this study. We hope to elicit these perspectives in future research.

Conclusions

Children with DIPG experience a multitude of symptoms requiring intensive multidisciplinary end-of-life care. This paper describes the choices made for these children and discusses how these choices influence our institutional model for palliative care. We believe this approach will be useful to clinicians caring for similar patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration. For this type of study, formal consent is not required.

References

1. Hargrave D, Bartels U, Bouffet E (2006) Diffuse brainstem glioma in children: critical review of clinical trials. Lancet Oncol 7:241–248
2. Warren KE (2012) Diffuse intrinsic pontine glioma: poised for progress. Front Oncol 2:205
3. Jansen MH, van Vuurden DG, Vandertop WP, Kaspers GJ (2012) Diffuse intrinsic pontine gliomas: a systematic update on clinical trials and biology. Cancer Treat Rev 38:27–35
4. Barkovich AJ, Krischer J, Kun LE, Packer R, Zimmerman RA, Freeman CR, Wara WM, Albright L, Allen JC, Hoffman HJ (1990) Brain stem gliomas: a classification system based on magnetic resonance imaging. Pediatr Neurosurg 16:73–83
5. Veldhuijzen van Zanten SE, van Meerwijk CL, Jansen MH, Twisk JW, Anderson AK, Coombes L, Breen M, Hargrave OJ, Hemsley J, Craig F, Cruz O, Kaspers GJ, van Vuurden DG, Hargrave DR; SIOPE DIPG Network (2016) Palliative and end-of-life care for children with diffuse intrinsic pontine glioma: results from a London cohort study and international survey. Neuro-Oncology 18:582–588
6. Wolfe J, Grier HE, Klar N, Levin SB, Ellenbogen JM, Salem-Schatz S, Emanuel EJ, Weeks JC (2000) Symptoms and suffering at the end of life in children with cancer. N Engl J Med 342(5):326–333
7. Heath JA, Clarke NE, Donath SM, McCarthy M, Anderson VA, Wolfe J (2010) Symptoms and suffering at the end of life in children with cancer: an Australian perspective. Med J Aust 192:71–75
8. Tomlinson D, Bartels U, Gammon J, Hinds PS, Volpe J, Bouffet E, Regier DA, Baruchel S, Greenberg M, Barrera M, Llewellyn-Thomas H, Sung L (2011) Chemotherapy versus supportive care alone in pediatric palliative care for cancer: comparing the preferences of parents and health care professionals. CMAJ 183:E1252-8
9. Theunissen JM, Hoogerbrugge PM, van Achterberg T, Prins JB, Vernooij-Dassen MJ, van den Ende CH (2007) Symptoms in the palliative phase of children with cancer. Pediatr Blood Cancer 49:160–165
10. Bluebond-Langner M, Belasco JB, Goldman A, Belasco C (2007) Understanding parents' approaches to care and treatment of children with cancer when standard therapy has failed. J Clin Oncol 25:2414–2419
11. Bartels U, Wolff J, Gore L, Dunkel I, Gilheeney S, Allen J, Goldman S, Yalon M, Packer RJ, Korones DN, Smith A, Cohen K, Kuttesch J, Strother D, Baruchel S, Gammon J, Kowalski M, Bouffet E (2014) Phase 2 study of safety and efficacy of nimotuzumab in pediatric patients with progressive diffuse intrinsic pontine glioma. Neuro-Oncology 11:1554–1559
12. Sanderson A, Zurakowski D, Wolfe J (2013) Clinician perspectives regarding the do-not-resuscitate order. JAMA Pediatr 167:954–958
13. Dussel V, Kreicbergs U, Hilden JM, Watterson J, Moore C, Turner BG, Weeks JC, Wolfe J (2009) Looking beyond where children die: determinants and effects of planning a child's location of death. J Pain Symptom Manag 37:33–43
14. Kassam A, Skiadaresis J, Alexander S, Wolfe J (2014) Parent and clinician preferences for location of end-of-life care: home, hospital or freestanding hospice? Pediatr Blood Cancer 61:859–864
15. Kassam A, Sutradhar R, Widger K, Rapoport A, Pole JD, Nelson K, Wolfe J, Earle CC, Gupta S (2017) Predictors of and trends in high-intensity end-of-life care among children with cancer: a population-based study using health services data. J Clin Oncol 35:236–242
16. Ho TH, Barbera L, Saskin R, Lu H, Neville BA, Earle CC (2011) Trends in the aggressiveness of end-of-life cancer care in the universal health care system of Ontario, Canada. J Clin Oncol 29:1587–1591
17. Veldhuijzen van Zanten SE, Cruz O, Kaspers GJ, Hargrave DR, van Vuurden DG; SIOPE DIPG Network (2016) State of affairs in use of steroids in diffuse intrinsic pontine glioma: an international survey and a review of the literature. J Neurooncol 128:387–394
18. Bartels U, Bouffet E (2012) The use of dexamethasone In: Hoffman RI (ed.) Understanding the journey, a parent's guide to DIPG. American Childhood Cancer Organization, Bethesda, pp 139–152