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Symptoms and management of children with incurable cancer in mainland China

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ABSTRACT

Purpose: This study was designed to report information regarding symptomology of incurable pediatric cancer to promote proactive medicine and support for children and their families in the palliative phase in Mainland China.

Method: A multi-center retrospective cohort study including 205 children who died from incurable cancer between June 2008 and September 2013 were analyzed.

Results: An incurable diagnosis was confirmed between 0 and 1726 (median, 279) days from initial diagnosis with death occurring between 1 and 239(median, 83) days. The most frequent symptoms were fatigue (93.7%), pain (87.3%), and poor appetite (76.1%). The earliest symptoms were pain and fatigue. Children with leukemia and lymphoma also complained early of nausea/vomiting, and children with solid tumors complained early of disturbed sleep. Later in the palliative phase, altered consciousness and seizures were found in children with central nervous system tumors and solid tumors, while children with leukemia and lymphoma were found to have fever, diarrhea, and bleeding. However, these symptoms only persisted for a short time. DNR discussions were held in 89 cases (43.4%) at a median of 37 (range, 4–178) days before death. A total of 154 patients (75.1%) died at home and 51 patients (24.9%) in the hospital.

Conclusions: This study provides new knowledge about symptomology to health care professionals and parents of children in Mainland China. Given our results, an improved alternative care plan should be developed and implemented earlier to facilitate end-of-life planning.

1. Introduction

In 2018, approximately 25,000 children, ages 0–14 years, will be diagnosed with cancer in Mainland China (Zheng et al., 2015). Of these children, about half of them will eventually develop a terminal cancer, despite recent medical advances (Zheng et al., 2015; Ye et al., 2015). For these children, decreased suffering through palliative care is prioritized. Pediatric palliative care is led by local office-based pediatricians and specialized pediatric palliative care teams (PPCT) to promote the best possible quality of life for these children and their families(American Academy of Pediatrics, 2000; American Academy of Pediatrics, 2013; Ye et al., 2016a). In 2014, the World Health Organization (WHO) stressed the importance of an anticipatory care plan (ACP) in the pediatric palliative phase, requiring specific knowledge about disease symptomology(WHO Definition of Palliative Care, 2015). Prior research reported the frequency of cancer-related symptoms in children with various incurable tumors (Table 1) and specific symptoms such as pain, fatigue, and poor appetite have been recognized in terminally ill children (Hongo et al., 2003; Jalmsell et al., 2006; Goldman et al., 2006; Theunissen et al., 2007; Pritchard et al., 2008; Ye et al., 2017a, 2017b). However, the documented onset and duration of these symptoms are unclear or limited. If symptom onset and duration

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Table 1
Symptoms During Palliative Treatment in Children with Incurable Tumors Presented in the Literature.

Characteristics	Hongo et al.	Jalmsell et al.	Goldman et al.	Theunissen et al.	Pritchard et al.	Ye et al.
Year	2003	2006	2006	2007	2008	2017
Study type	Retrospective	Retrospective	Prospective	Retrospective	Retrospective	Retrospective
Number	28	449	164	32	52	205
Diagnosis	Leukemia,Lymphoma,brain tumor,solid tumor	Leukemia,Lymphoma,brain tumor,solid tumor	Leukemia,Lymphoma,brain tumor,solid tumor	Leukemia, brain tumor,solid tumor	Leukemia,Lymphoma,brain tumor,solid tumor	Leukemia,Lymphoma,brain tumor,solid tumor
Male: Female	16:12	NA	88:76	17:15	32:20	112:93
Age at initial diagnosis (range)	9.4(1.2–19.5)	NA	8.9(0.2–19.9)	NA	6.0(0.02–19.6)	6.1(0.6–17.6)
Symptoms,n (%)						
Poor appetite	28(100)	321(71.5)	111(67.7)	24(75.0)	20(38.5)	156(76.1)
Dyspnea	23(82.1)	172(38.3)	69(40.2)	13(40.6)	15(28.8)	63(30.7)
Pain	21(75.0)	328(73.1)	150(91.5)	24(75.0)	35(67.0)	179(87.3)
Fatigue	20(71.4)	386(86.0)	136(90.9)	23(71.9)	11(21.2)	192(93.7)
Nausea/vomiting	16(57.1)	279(62.1)	94(57.6)	17(53.1)	7(13.5)	98(47.8)
Constipation	13(46.4)	178(39.6)	96(58.5)	11(34.4)	7(13.5)	106(51.7)
Altered consciousness	10(35.7)	NA	42(25.6)	12(37.5)	3(5.8)	77(37.6)
Diarrhea	6(21.4)	NA	22(13.4)	9(28.1)	NA	39(19.0)
Reduced mobility	NA	341(75.9)	100(61.0)	21(65.6)	28(53.8)	134(65.4)
Seizures	NA	NA	36(22.0)	1(3.2)	4(7.7)	63(30.7)
Vision/hearing deficits	NA	154(34.3)	56(34.1)	2(6.3)	6(11.5)	57(27.8)
Disturbed sleep	NA	239(53.2)	106(64.7)	8(25.0)	11(21.2)	146(71.2)
Excess secretions	NA	NA	65(39.6)	NA	3(5.8)	34(16.6)
Fever	NA	NA	53(32.3)	NA	3(5.8)	41(20.0)
Bleeding	NA	NA	51(31.1)	12(37.5)	4(7.7)	32(15.6)

NA, not available.

are known, an ACP that targets symptom management could be established. The plan would cover preset medication and proactive supportive care, resulting in fewer hospitalizations and a maximized quality of life (Liben et al., 2008; Ye et al., 2017c). ACPs also provide parents more time to cope with expected challenges and make end-of-life decisions. Furthermore, ACPs may allow children to die at home. This is very important to the Chinese society of Confucianism (Vickers et al., 2007; Wolfe et al., 2008). It is believed that the spirit of the dead will suffer after death if the spirit died in an unfamiliar place, such as a hospital away from home (Ye et al, 2016b, 2017d). This study describes the specific trajectories of cancer-related symptoms in four incurable cancers (central nervous system tumor, leukemia, lymphoma, and solid tumors), pain medication and its effect in palliative care, and the feasibility of do-not-resuscitate (DNR) orders in Mainland China.

2. Methodology

2.1. Patients

The patients enrolled in this study died from an incurable tumor between June 2008 and May 2013, and were treated at the First Affiliated Hospital of Guangzhou University of Chinese Medicine, the Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Sun Yat-sen University Cancer Center, and the Affiliated Tumor Hospital of Guangzhou Medical University. The palliative phase began when the parents were informed by their primary oncologist that a cure for their child was impossible and that subsequent treatment would be given without curative intent. The pediatric oncologist recorded the date, the options and choices of palliative care that had been discussed in the medical record. This retrospective study was reviewed by medical ethical boards from all participating hospitals. Informed parental consent was not required before patient enrollment due to its retrospective nature of this study.

2.2. Methods

The patients were identified from the databases of the four hospitals: the First Affiliated Hospital of Guangzhou University of Chinese Medicine (between June 2008 and May 2011), the Second Affiliated Hospital of Guangzhou University of Chinese Medicine (between March 2009 and February 2012), Sun Yat-sen University Cancer Center (between September 2011 and May 2013), and the Affiliated Tumor Hospital of Guangzhou Medical University (between April 2010 and March 2012). The inclusion criteria required the selection of patients younger than 18 years of age at the time of the confirmed cancer diagnosis. The medical charts and nursing recording sheets included basic demographics (age, sex, insurance information, etc.) and cancer-related documentation (tumor type, treatment protocol, duration of palliative care, etc.). The recording of symptoms' incidence began when the palliative care plan was initiated. Dr Zhang and Dr Liang independently reviewed the medical charts and nursing recording sheets. Dr. Ye was advised of potential conflicting information and the patients' primary oncologists would be contacted if necessary information was missing. The medical charts and nursing recoding sheets reviewed refer to a period of five years and comprise that of four hospitals, and a structured table was developed by the authors to solve the inconsistent records between each hospital and year, which included five parts: demographics and clinical characteristics of the children, symptom onset and duration (a checklist to systematically identify the symptoms experienced and professional attention of health professionals during the palliative phase), symptom management plan (medicine administration, nursing care, etc), the DNR discussion (timing, the concerns for agreement or rejection, etc), and the parents’ preferred location for death. In addition, records of the oncology meetings with parents were also analyzed to acquire more disease-related information and end-of-life decisions.

2.3. Statistical analysis

Baseline characteristics, including demographics and clinical characteristics, were examined by the Pearson chi-square test or Fischer exact test. The symptoms of central nervous system tumors, leukemia, lymphoma, and solid tumors were analyzed by odds ratios with an associated 95% confidence interval. Children with central nervous system tumors were applied as a reference category. P-values ≤ 0.05 were considered significant. Software calculations were conducted with SPSS statistical package (Version 17) and Stata (Version 11).

3. Results

3.1. Subjects and treatment

A total of 205 patients from the four hospitals were included. The sample contained 112 males and 93 females ranging from 7 months to 17.6 years (median, 6.8 years) at the time of the initial diagnosis. Of the 205 patients, 71 patients were diagnosed with a central nervous system tumor, 42 patients with leukemia, 55 patients with lymphoma, and 37 patients with a solid tumor. Palliative care began after a median 279 days from initial diagnosis (range, 0–1726 days).The primary documented reasons to start palliative care were treatment progression (46.8%) and recurrence after complete remission (37.1%).Patients with central nervous system tumors were more likely to be younger (P = 0.0012), more likely have an incurable cancer diagnosis at the beginning than other types of tumor(P = 0.0323), have a longer palliative care phase (P = 0.0089), and were more likely to die in the hospital (P = 0.0675).The delivery of cancer-directed chemotherapy in the palliative care phase was administered to 103 patients (50.2%) with a median duration of 37 days (range, 4–172 days). 62 patients (30.2%) received radiotherapy with a median duration of 19 days (range, 2–88 days). Of the 205 patients, 16 (7.8%) received surgery(including craniotomies, bone marrow transplants, etc). Other demographics and clinical characteristics, including treatments, are presented in Table 2.

3.2. Frequency and risks of symptoms

The 15 most frequent symptoms in the medical charts were fatigue (93.7%), pain(76.1%), poor appetite(71.2%), disturbed sleep(65.4%), reduced mobility (51.7%), constipation (47.8%), nausea/vomiting(37.6%), altered consciousness(30.7%), dyspnea (30.7%), seizures (27.8%), vision/hearing deficits(20.0%), fever(19.0%), diarrhea(16.6%), excess secretions (15.6%) and bleeding(15.6%). Compared to children with central nervous system tumors, children with leukemia were found to have more pain (OR = 5.36, 95%CI: 1.16–24.75), poor appetite (OR = 2.61, 95%CI:1.05–6.46), fever(OR = 4.57, 95%CI:1.67–12.55), diarrhea (OR = 6.70, 95%CI:2.01–22.49) and bleeding (OR = 9.07,95%CI:2.38–34.49). Children with lymphoma were more likely to have a poor appetite (OR = 3.14, 95%CI:1.33–7.41), fever (OR = 3.43, 95%CI:1.29–9.14), diarrhea(OR = 6.87, 95%CI:2.14–22.02), and bleeding (OR = 5.67, 95%CI:1.49–21.46). Children with solid tumors were more likely to have a poor appetite (OR = 3.93, 95%CI:1.36–11.31),constipation(OR = 3.05, 95% CI:1.31–7.11), dyspnea(OR = 2.26, 95%CI:0.99–5.13), diarrhea(OR = 3.91, 95%CI:1.06–14.37).Children with central nervous system tumors were more like to have reduced mobility(OR = 0.23, 95%CI:0.10–0.49) compared to children with lymphoma, disturbed consciousness (OR = 0.05, 95%CI:0.02–0.13) compared to children with lymphoma, seizures (OR = 0.35, 95% CI:0.15–0.84) compared to children with leukemia, vision/hearing deficits (OR = 0.20, 95%CI:0.08–0.50) compared to children with solid tumors, and excess secretions(OR = 0.11, 95%CI:0.03–0.50) compared to children with leukemia. More specific symptomology is presented in Table 3.

Table 2
Patient characteristics categorized by tumor type.

Characteristics	CNS Tumors	Leukemia	Lymphoma	Solid Tumors	Total	P value
No.	71	42	55	37	205	NA
Age at initial diagnosis						0.0012
Median, y	4.1	5.7	8.1	7.7	6.8	
Range, y	0.6–9.3	1.3–10.2	2.0–14.6	0.9–17.6	0.6–17.6	
Gender						0.5413
Male, n (%)	42(59.2)	19(45.2)	31(56.4)	20(54.1)	112(54.6)	
Female, n (%)	29(40.8)	23(54.8)	24(43.6)	17(45.9)	93(45.4)	
Residence						0.1063
City dweller	44(62.0)	18(42.9)	24(43.6)	21(56.8)	107(52.2)	
Rural dweller	27(38.0)	24(57.1)	31(56.4)	16(43.2)	98(47.8)	
Health medicare						0.9613
New rural cooperative health care system	55(77.5)	36(85.7)	44(80.0)	30(81.1)	165(80.5)	
Commercial insurance	11(15.5)	4(9.5)	7(12.7)	4(10.8)	26(12.7)	
None	5(7.0)	2(4.8)	4(7.3)	3(8.1)	14(6.8)	
Time since initial diagnosis to incurable disease						0.0151
Median, d	146.5	408	324	216.5	279	
Range, d	0–711	0–1726	0–1435	0–957	0–1726	
Reason for start palliative care						0.0323
Incurable from diagnosis, n (%)	18(25.4)	3(7.1)	6(10.9)	6(16.2)	33(16.1)	
Progression during treatment, n (%)	33(46.5)	17(40.5)	25(45.5)	21(56.8)	96(46.8)	
Recurrence after CR, n (%)	20(28.1)	22(52.4)	24(53.3)	10(27.0)	76(37.1)	
Anticancer therapy in palliative care						0.1384
Chemotherapy, n (%)	31(43.7)	26(61.9)	29(52.7)	17(45.9)	103(50.2)	
Duration, d(range)	47(4–121)	32(10–142)	41(26–172)	46(9–131)	37(4–172)	
Radiotherapy, n (%)	22(31.0)	9(21.4)	14(25.5)	17(45.9)	62(30.2)	
Duration, d(range)	21(2–65)	14.5(7–43)	17(4–51)	37(10–88)	19(2–88)	
Surgery, n (%)	9(12.7)	3(7.1)	3(5.5)	1(2.7)	16(7.8)	
Duration of palliative care						0.0089
Median, d	106	59	81	95	83	
Range, d	2–239	6–159	1–207	5–172	1–239	
Death location						0.0675
At home, n (%)	47(66.2)	35(83.3)	46(83.6)	26(70.3)	154(75.1)	
In hospital, n (%)	24(33.8)	7(16.7)	9(16.4)	11(29.7)	51(24.9)	

Abbreviations: CNS, central nervous system; **CR**, complete remission; **NA,** not available.

3.3. Onset and duration of symptoms

The onset of cancer-related symptoms was defined as the first time a specific symptom was recorded in the medical chart (Fig. 1).Inpatients with central nervous system tumors, the earliest and most prolonged symptoms were pain(median onset of 80 days before death; range, 4–239 days), fatigue(median onset of 75 days before death; range, 2–197 days) and nausea/vomiting(median onset of 96 days before death; range, 11–216 days).Late-occurring symptoms with the shortest duration were altered consciousness (median onset of 26 days before death; range, 6–88 days), seizures(median onset of 33 days before death; range, 5–85 days) and vision/hearing deficits (median onset of 37 days before death; range, 6–119 days).In patients with leukemia, the earliest and most prolonged symptoms were nausea/vomiting (median onset of 74 days before death; range, 13–159 days), constipation (median onset of 67 days before death; range, 9–131 days),and fatigue (median onset of 53 days before death; range, 8–145 days).Late-occurring symptoms with the shortest duration were bleeding (median onset of 15 days before death; range, 6–83 days),diarrhea(median onset of 22 days before death; range, 12–95 days), and fever(median onset of

Table 3
ORs and 95CIs for a specific symptom during the last month of life in children with various tumors as compared with children with CNS tumors.

Symptoms n (%)	CNS Tumors (N = 71)	Leukemia (N = 42)	OR(95%CI)	Lymphoma (N = 55)	OR(95%CI)	Solid Tumors (N = 37)	OR(95%CI)	Total (N = 205)
Fatigue	63(88.7)	41(97.6)	5.21(0.63–43.19)	54(98.2)	6.86(0.83–56.58)	34(91.9)	1.44(0.36–5.78)	192(93.7)
Pain	56(78.9)	40(95.2)	5.36(1.16–24.75)^{a}	49(90.7)	2.19(0.79–6.08)	34(91.9)	3.03(0.82–11.26)	179(87.3)
Poor appetite	44(62.0)	34(81.0)	2.61(1.05–6.46)^{a}	46(83.6)	3.14(1.33–7.41)^{b}	32(86.5)	3.93(1.36–11.31)^{b}	156(76.1)
Disturbed sleep	53(74.6)	26(61.9)	0.55(0.24–1.25)	35(63.6)	0.59(0.28–1.28)	32(86.5)	2.17(0.74–6.42)	146(71.2)
Reduced mobility	65(91.5)	22(52.4)	0.10(0.04–0.29)^{c}	19(34.5)	0.05(0.02–0.13)^{c}	28(75.7)	0.29(0.09–0.88)^{a}	134(65.4)
Constipation	31(43.7)	18(42.9)	0.97(0.45–2.09)	31(56.4)	1.67(0.82–3.39)	26(70.3)	3.05(1.31–7.11)^{b}	106(51.7)
Nausea/vomiting	29(40.8)	20(47.6)	1.32(0.61–2.84)	28(50.9)	1.50(0.74–3.05)	21(56.8)	1.90(0.85–4.25)	98(47.8)
Disturbed consciousness	41(57.7)	11(26.2)	0.26(0.11–0.60)	13(23.6)	0.23(0.10–0.49)^{c}	12(32.4)	0.35(0.15–0.81)^{a}	77(37.6)
Dyspnea	21(29.6)	10(23.8)	0.74(0.31–1.78)	14(25.5)	0.81(0.37–1.80)	18(48.6)	2.26(0.99–5.13)^{a}	63(30.7)
Seizures	31(43.7)	9(21.4)	0.35(0.15–0.84)^{a}	11(20.0)	0.32(0.14–0.73)	12(32.4)	0.62(0.27–1.43)	63(30.7)
Vision/hearing impaired	41(57.7)	5(11.9)	0.11(0.04–0.28)^{c}	3(5.5)	0.04(0.12–0.15)^{c}	8(21.6)	0.20(0.08–0.50)^{c}	57(27.8)
Fever	7(9.9)	14(33.3)	4.57(1.67–12.55)^{b}	15(27.3)	3.43(1.29–9.14)^{a}	5(13.5)	1.43(0.42–4.86)	41(20.0)
Diarrhea	4(5.6)	12(28.6)	6.70(2.01–22.49)^{c}	16(29.1)	6.87(2.14–22.02)^{c}	7(18.9)	3.91(1.06–14.37)^{a}	39(19.0)
Excess secretions	22(31.0)	2(4.8)	0.11(0.03–0.50)^{c}	3(5.5)	0.13(0.04–0.46)^{c}	7(18.9)	0.52(0.19–1.36)	34(16.6)
Bleeding	3(4.2)	12(28.6)	9.07(2.38–34.49)^{c}	11(20.0)	5.67(1.49–21.46)^{b}	4(10.8)	2.75(0.58–12.99)	32(15.6)

a), $P < 0.05$**; b),** $P < 0.01$**; c),** $P < 0.001$.

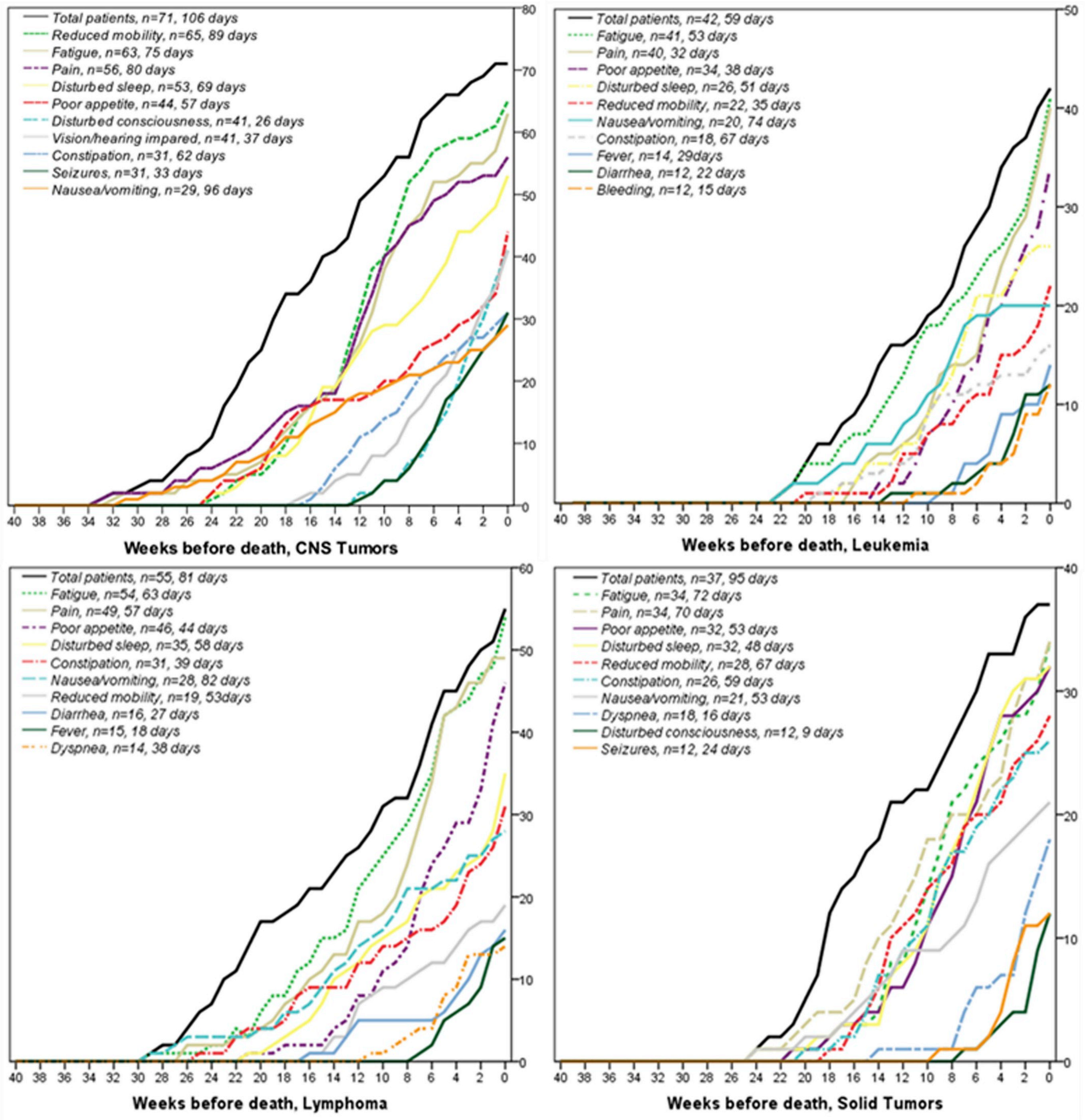

Fig. 1. Timing and duration of cancer-related symptoms in the palliative phase(revised).

29 days before death; range, 7–69 days). In patients with lymphoma, the earliest and most prolonged symptoms were nausea/vomiting (median onset of 82 days before death; range, 23–207 days), fatigue (median onset of 63 days before death; range, 7–199 days) and pain (median onset of 57 days before death; range, 4–202 days). Late-occurring symptoms with the shortest duration were fever(median onset of 18 days before death; range, 1–55 days), dyspnea (median onset of 38 days before death; range, 3–81 days) and diarrhea(median onset of 27 days before death; range, 6–115 days). In patients with solid tumors, the earliest and most prolonged symptoms were pain (median onset of 70 days before death; range, 6–172 days), poor appetite (median onset of 53 days before death; range, 11–154 days), and disturbed sleep (median onset of 48 days before death; range, 9–161 days). Late-occurring symptoms with the shortest duration were altered consciousness (median onset of 9 days before death; range, 5–58 days), seizures (median onset of 24 days before death; range, 13–71 days) and dyspnea (median onset of 16 days before death; range, 5–102 days).

3.4. Pain and pain management

A total of 179 patients (87.3%) in the palliative phase reported symptoms of pain that started as early as a median of 64 days (range, 4–239 days) before death and lasted a median of 51 days (range, 7–109 days) in the palliative phase. The loci of pain primarily included the

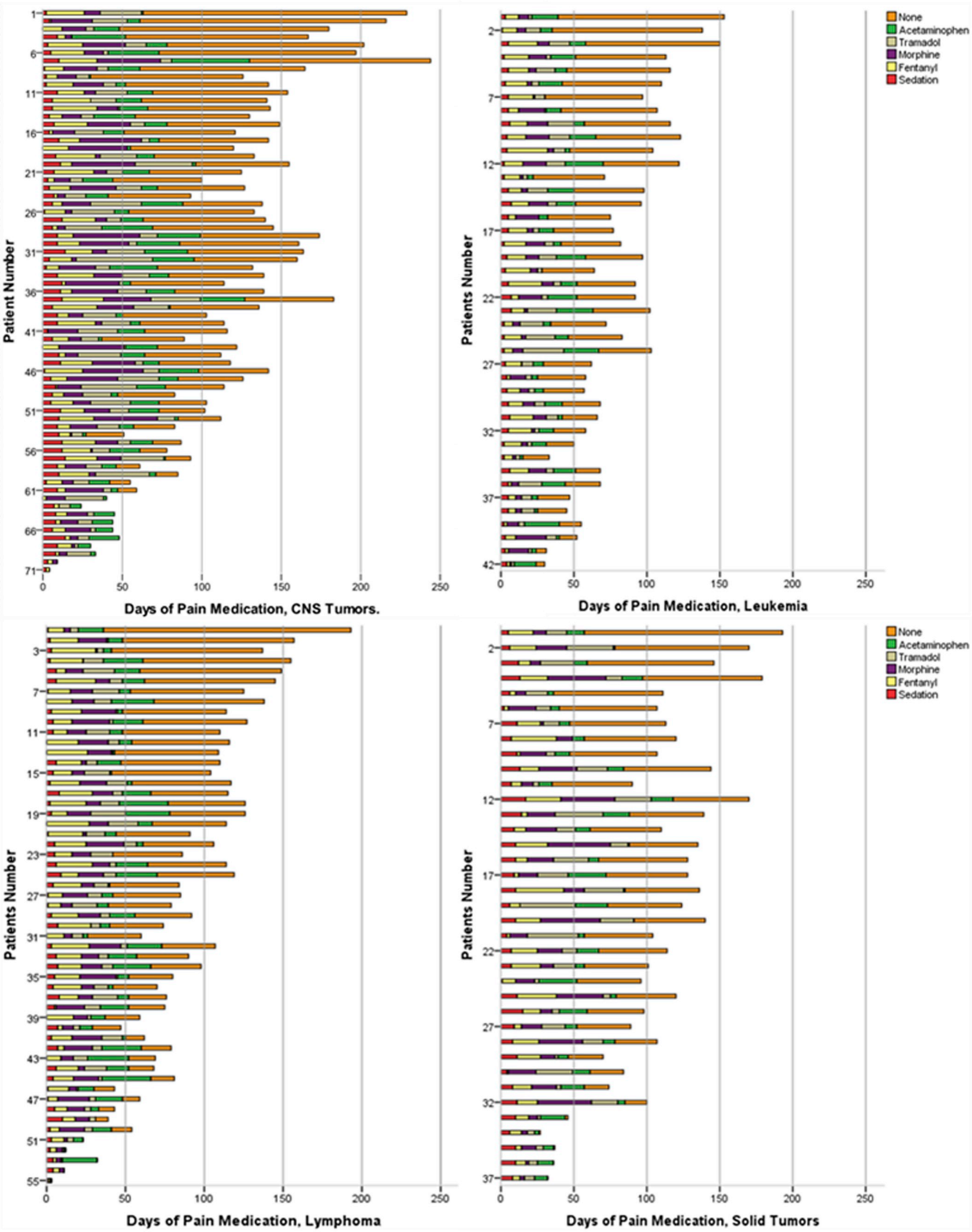

Fig. 2. Pain medication during the palliative phase.

head(42.4%), abdomen(19.5%), back(14.1%), spine(8.3%), neck (5.9%), and legs(3.4%). Pain management protocols were specific to each patient in the palliative phase and are represented in Fig. 2. We independently analyzed five of the commonly used pain medicines: acetaminophen, tramadol, morphine, fentanyl, and midazolam (administered to sedation). In patients with central nervous system tumors, pain medication was administered a median of 46 days (range, 3–137 days) in the palliative care. Acetaminophen was administered a median of 17 days(range, 0–51 days), tramadol 11 days(range, 0–43 days), morphine18 days(range, 1–39 days), fentanyl 13 days(range, 0–28 days), and midazolam 7 days(range, 0–16 days).In patients with leukemia, pain medication was administered a median of 37 days (range, 1–92 days)in the palliative care. Acetaminophen was administered a median of 10 days(range, 0–31 days), tramadol 6 days(range, 0–24 days), morphine 7 days(range, 0–18 days), fentanyl 11 days(range, 2–36 days), and midazolam 4 days(range, 1–9 days). In patients with lymphoma, pain medication was administered a median of 41 days (range, 2–119 days) in the palliative care. Acetaminophen was administered a median of 9 days(range, 0–31 days), tramadol 7 days (range, 0–22 days), morphine 11 days(range, 0–24 days), fentanyl 13 days(range, 1–37 days) and midazolam 3 days(range, 0–10 days). In patients with solid tumors, pain medication was administered a median of 59 days (range, 5–153 days) in the palliative care. Acetaminophen was administered after a median of 8 days(range, 0–26 days), tramadol 11 days(range, 0–38 days), morphine 16 days(range, 1–43 days), fentanyl 12 days(range, 1–33 days), and midazolam 9 days(range, 0–17 days).In addition, 62 patients(30.2%) were administered dexamethasone as adjuvant pain medicine.

3.5. *DNR discussions and death location*

DNR discussions with the parents, with or without the patient, were held in 89 cases (43.4%) after a median of 18 days (range, 0–121 days) from the beginning of palliative care and a median of 37 days (range, 4–178 days) before the patients' death. Of the 89 cases, 28 patients (13.7%; median age of 13 years) joined the decision-making process with their parents. Death occurred at a median of 83 days (range, 1–239 days) from the beginning of palliative care. A total of 154 patients (75.1%) died at home and 51 (24.9%) at hospital. Of the patients who died at hospital, 37 (18.0%) died in the pediatric or oncology department and 14 (6.9%) died in the intensive care unit. A total of 138 patients (67.3%) died during sleep or in a state of somnolence.

4. Discussion

This study provides insight into the onset and duration of specific symptoms in children with various incurable tumors during palliative care. Pain, fatigue, and poor appetite were the most frequent symptoms recorded in previous research and this study confirms these findings (Hongo et al., 2003; Jalmsell et al., 2006; Goldman et al., 2006; Theunissen et al., 2007; Pritchard et al., 2008; Ye et al., 2017e). Furthermore, we found that symptoms of pain, fatigue and nausea/vomiting in the palliative phase began earlier and last longer in all cancer types. Notably, children with leukemia frequently complained of constipation and children with solid tumors frequently complained of disturbed sleep. Altered consciousness and seizures were frequently occurred later in the palliative phase and lasted for a relatively short time in the patients with central nervous system tumors and solid tumors. Patients with central nervous system tumors were found to have vision/hearing deficits later in the palliative phase. Bleeding, fever, and diarrhea frequently occurred in patients with leukemia and lymphoma. This was a late finding and typically lasted for few days. This information provides physicians and nurses with more considerable references regarding symptom onset, duration, and the need for intervention. This data may also help to guide parents' expectations of disease etiology. Given the information in this study, parents may also preserve their child's quality of life and avoid unnecessary suffering with advance care plans (Hammes et al., 2005).

Pain management is important to pediatric palliative care. Signs and known symptoms of pain are associated with a parent's feelings of grief after a child's death (Kreicbergs et al., 2005). The occurrence of pain was higher, relative to any other symptom in our study. This may indicate that pain management protocols in these hospitals should be enhanced. However, high occurrences of pain may also be attributed to a lack of availability pain medication for patients' receiving palliative care at home in Mainland China (Ye et al., 2018a). Prescription drugs, especially pain medications, are strictly controlled out of the hospital and patients may not have been able to obtain the necessary medications at home.

DNR discussions were performed for 89 cases (43.4%) at a median of 37 days (range, 4–178 days) before the patients' death. This is similar to the median 39 days in Gofton's report (Gofton et al., 2012). Early DNR discussions are an important component of pediatric palliative care and may help parents to stay with their child at home in his or her final days of life. The rate of DNR discussions with Chinese parents is relatively low compared to the 70% reported by Gofton and 100% reported by Jagt's (Gofton et al., 2012; Charissa et al., 2015). This may be due to the Chinese culture and the reluctance to talk about one's death when one is still living (Chou et al., 2013; Ye et al., 2018b, 2018c). Furthermore, we found that younger parents with a higher education are more willing to negotiate with physician about the DNR and euthanasia (though it is lawfully prohibited in mainland China) according to notes from the medical records. Death occurred at a median of 83 days (range, 1–239 days) after the start of palliative care. A total of 154 patients (75.1%) died at home. This is a higher rate compared to reports from the United States (44%–57%), Canada (35%), and Germany (40%).Though the DNR rate in this study is low (43.4%), the home death rate indicates that there is great potential for more frequent DNR discussions in Chinese families and at an earlier stage of palliative care, despite the cultural barriers (Groh et al., 2013; Wolfe et al., 2000; Mack et al., 2005). However, China saw the increasing tension between doctors and the patients as well as their relatives mainly due to unrealistic expectation of the medical treatment in recent years (Li et al., 2011; Wang et al., 2004; Qiu et al., 2017). The unsatisfied patients especially the family members would harm or even kill their doctors in various ways and some serious discussions such as DNRs should be performed very carefully by Chinese oncologists in recent years. Thus, in pediatric palliative care, DNRs are recommended when the trust between the oncologists and the parents are well established.

4.1. *Strengths and limitations*

This is the first study to provide the timeline for cancer-related symptoms in pediatric patients with incurable tumors in the palliative phase in Mainland China. It improves our knowledge of the onset of symptoms and symptom duration before death. In pediatric oncology, previous studies are often dependent on answers provided by the parents. These studies are therefore at risk for recall bias (James and Johnson, 1977; Wheeler, 2001). In this study, all symptoms are retrieved from the medical charts instead of questionnaires answered by parents, minimizing recall bias. However, some other limitations of this study should be considered. First, the data are collected retrospectively and further prospective studies are indicated to substantiate the symptomologies identified in this study. Second, the palliative phase is variable between studies because of the undefined transition from curative care to palliative care (Kreicbergs et al., 2004; Browning, 2002). Therefore, the comparability between studies is limited. Third, we do not evaluate the severity of symptoms, nor the psychological symptoms, such as anxiety, depression, and fear of death in this study. We acknowledge that these variables are considerable and important to the children's quality of life. Fourth, the medical charts analyzed in this study are those with few missing data and some charts with low quality (lots of missing data) were excluded, which will result in a bias to the results and conclusions. Thus, future studies should include more patients in order to make a more robust conclusion. Fifth, suffering at the end-of-life and quality-of-life are not only determined by counting and rating the number of symptoms and duration but also by their relevance to the patient and parents. At last, symptoms like fatigue, poor appetite or constipation were not fully understood in the palliative care and more researches should be warranted to develop standardized interventions for these symptoms.

5. Conclusion

This multi-institutional study identified the trajectories of some most frequent symptoms of children with incurable tumor in the palliative phase. The pain management for children was poor and Do Not Resuscitate discussion with Chinese parents was feasible despite of cultural barriers. Given our results, an improved alternative care plan might be developed and implemented earlier to facilitate end-of-life planning.

Conflicts of interest

The authors have no conflicts of interest to disclose.

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