Current Status of Aggressive End-of-Life Care in Children with Hematologic Malignancy: A Population Based Study

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Abstract

Background: Hematologic malignancies are the most frequent type of cancer in children but limited data are available regarding the quality of end-of-life care (EOLC) for children with hematologic malignancies. The aims of this study were (i) to compare aggressive EOLC between children with hematologic malignancies and those with solid tumors; and (ii) to describe factors associated with aggressive EOLC in children with hematologic malignancies.

Methods: We retrospectively reviewed 0- to 18-year-old patients with cancer, who died between April 2012 and March 2016 in Japan using the Diagnosis Procedure Combination per-diem payment system. Indicators of aggressive inpatient EOLC were defined as intensive care unit admission, cardiopulmonary resuscitation (CPR), intubation and/or mechanical ventilation, hemodialysis, or extra-corporeal membrane oxygenation in the last 30 days of life, or intravenous chemotherapy in the last 14 days. We determined factors associated with aggressive EOLC using regression models. Data regarding use of blood transfusion were also obtained from the database.

Results: Among 1199 patients, 433 (36%) had hematological malignancies. Children with hematologic malignancies were significantly more likely than those with solid tumors to have intubation and/or mechanical ventilation (37.9% vs. 23.5%), intensive care unit admission (21.9% vs. 7.2%), CPR (14.5% vs. 7.7%), hemodialysis (13.2% vs. 3.1%) or extra-corporeal membrane oxygenation (2.5% vs. 0.4%) in their last 30 days, or intravenous chemotherapy (47.8% vs. 18.4%; all $P < .01$) within their last 14 days of life. Over 90% of children with hematological malignancies received a blood transfusion within the last 7 days of life. For hematological malignancies, age under 5 years was associated with CPR and ≥2 aggressive EOLC indicators. Longer hospital stays had decreased odds of ≥2 aggressive EOLC indicators.

Conclusion: Children with hematologic malignancies are more likely to have aggressive EOLC compared to those with solid tumors. A younger age and shorter hospital stay might be associated with aggressive EOLC in children with hematologic malignancies.

Introduction

Hematologic malignancies are the most frequent type of cancer in children, accounting for over 40% of childhood cases. The outcomes for children with hematologic malignancies have dramatically improved over the last several decades and the five-year survival rate of hematologic malignancy is about 80%-90% in high-income countries.[1,2] However, about 10%-20% of children will die due to these malignancies.

Many adults who are diagnosed with malignancies may express their wish to avoid life-extending measures at their end-of-life (EOL).[3,4] However, in the adult setting, patients with hematologic malignancies are less likely to receive palliative care[5] and more likely to accept intensive anti-cancer treatments until EOL, which is different than for patients with solid tumors.[6] Transfusions and other therapies may result in abridged eligibility for admission to a hospice,[7–8] creating a burden for those

staying at home,[9] and may result in admission to hospital until death. Compared to death at home, hospital deaths pose a risk of having suboptimal quality of life for patients and increased potential for caregiver's less than optimum grief process.[10,11]

Children with advanced cancer have been shown to experience a much higher rate of aggressive medical care at their EOL than adults,[12] so children with hematologic malignancies might be treated with more intensive treatments until their EOL. However, only limited data from single center studies are available regarding the aggressive EOL care (EOLC) among children with hematologic malignancies.[13,14]

The aims of this national Japanese study were (i) to equate aggressive EOLC between children with hematologic malignancies and those with solid tumors; and (ii) to describe factors associated with aggressive EOLC in children with hematologic malignancies. The findings will lead to the creation of guidelines for future EOL planning.

Methods

Data source

In this retrospective cohort study, data were extracted from the Diagnosis Procedure Combination per-diem payment system (DPC/PDPS), a national inpatient database in Japan. The DPC/PDPS is a case-mix patient classification system that is linked to payments at acute-care and mixed-care hospitals in Japan. By 2016, more than 1,600 hospitals have adopted the DPC/PDPS-based reimbursement system, accounting for more than half of the 894 000 beds in the country. [15]

Anonymous clinical and administrative claims data were collected annually for patients from the participating hospitals. Clinical data were collected based on baseline patient characteristics, diagnosis (based on International Statistical Classification of Diseases and Related Health Problems, 10th revision [ICD-10]), major or minor procedures, medications, use of medical materials, admission and discharge information such as the reason for admission, discharge disposition and outcome at the hospital discharge. The DPC/PDPS also includes information about the hospital, such as the number of beds.

The Institutional Review Board of the Tokyo Medical and Dental University and the National Center for Child Health and Development approved this study. The boards determined that the requirement for informed consent from patients was unnecessary because the data were anonymous.

Participants and variables

The study population consisted of patients in the DPC database with an oncologic diagnosis, aged 0 to 18 years at the time of their death, who died between April 2012 and March 2016 (fiscal year 2012 to 2015). An oncologic diagnosis was defined by ICD-10, including malignant neoplasms (C00-C97), but excluding in situ neoplasms (D00-D09) and benign neoplasms (D10-D36). We could not use the International Classification of Diseases for Oncology (ICD-O-3) due to the unavailability of data.

We collected the data including age, sex, admission status (urgent or non-urgent), and cancer type according to ICD-10 from the database. Age at death was categorized into 4 groups: 0–4, 5–9, 10–14 and 15–18 years. Cancer type was categorized based on hematologic malignancies (C80-C97), CNS tumors (C70-C72), and other solid tumors (other ICD-10 codes). Hospital characteristics included length of hospital stay (0–29, 30–119, 120 + days), hospital type (university hospital or other) and number of childhood deaths per year (1–5, 6–11, 12–16, 17+). Data regarding use of intensive care unit (ICU), cardiopulmonary resuscitation (CPR), intubation, mechanical ventilation, hemodialysis, extra-corporeal membrane oxygenation (ECMO), tracheostomy placement, gastrostomy placement, chemotherapy, and blood transfusion were also obtained from the database.

We defined indicators of aggressive inpatient EOLC according to previous studies in adults and pediatric patients with cancer[12,16–19] and after discussions with two oncologists, two palliative care physicians, and one statistician. The indicators were ICU admission, CPR, intubation and/or mechanical ventilation, hemodialysis, or ECMO in the last 30 days of life, or intravenous chemotherapy in the last 14 days of life.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD) or median and interquartile range (IQR), depending on the overall variable distribution. Descriptive statistics were calculated for each independent and dependent variable according to the type of cancer. Multilevel logistic regression models were constructed to determine factors associated with: (1) ≥ 1 aggressive EOLC indicator; (2) ≥ 2 aggressive EOLC indicators; (3) CPR; and (4) intravenous chemotherapy. Statistical analyses were conducted using R statistical software v 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Participant characteristics

Table 1 shows the characteristics of the study population. Among 1199 patients, 433 (36%) had hematological malignancies. The mean age (SD) of children with hematological malignancies and solid tumors was 10.3 (6.2) and 10.3 (5.8) years, respectively. We found no significant difference in hospital characteristics between children with hematological malignancies and those with solid tumors except for the length of hospital stay (Table 1).

Table 1
Characteristics of study patients and hospitals

	All[a] (n = 1199)	Hematologic malignancy[a] (n = 433)	Solid tumor[a] (n = 766)	*P*-value
Patient characteristics				
Age at death (years)				.07
0-4	253 (21.1)	100 (23.1)	153 (20.0)	
5-9	266 (22.2)	78 (18.0)	188 (24.5)	
10-14	263 (21.9)	97 (22.4)	166 (21.7)	
15-18	417 (34.8)	158 (36.5)	259 (33.8)	
Gender, female	529 (44.1)	175 (40.4)	354 (46.2)	.06
Cancer type				
Hematologic malignancy	433 (36.1)	433 (100)	0 (0)	
CNS tumor	307 (25.6)	0 (0)	307 (40.1)	
Other solid tumor	459 (38.3)	0 (0)	459 (59.9)	
Urgent admission	245 (20.4)			
Hospital characteristics				
Hospital type				.40
University hospital	765 (63.8)	269 (62.1)	496 (64.8)	
Other hospital	434 (36.2)	164 (37.9)	270 (35.2)	
Length of hospital stay (days)				<.01
0-29	401 (33.4)	94 (21.7)	307 (40.1)	
30-119	408 (34.0)	147 (33.9)	261 (34.1)	
120+	390 (32.5)	192 (44.3)	198 (25.8)	
Number of childhood deaths per year				.34
1-5	298 (24.9)	101 (23.3)	197 (25.7)	
6-11	301 (25.1)	110 (25.4)	191 (24.9)	
12-16	306 (25.5)	104 (24.0)	202 (26.4)	
17+	294 (24.5)	118 (27.3)	176 (23.0)	

Year of death				.53
2012-2013	607 (50.6)	225 (52.0)	382 (49.9)	
2014-2015	592 (49.4)	208 (48.0)	384 (50.1)	
[a]Data indicate number of patients (%), unless otherwise indicated.				

Aggressive EOLC indicators for children with hematologic malignancies compared to those with solid tumors

The most common aggressive EOLC indicators were intravenous chemotherapy (29.0%) and intubation and/or mechanical ventilation (28.7%). We found significant differences in the aggressive EOLC indicators between children with hematologic malignancies and those with solid tumors (Table 2). In the last 30 days of life, children with hematologic malignancies were significantly more likely to have intubation and/or mechanical ventilation (37.9% vs. 23.5%; $P < .01$), ICU admission (21.9% vs. 7.2%; $P < .01$), CPR (14.5% vs. 7.7%; $P < .01$), hemodialysis (13.2% vs. 3.1%; $P < .01$), or ECMO (2.5% vs. 0.4%; $P < .01$), than those with solid tumors. In addition, children with hematological malignancies were significantly more likely to receive intravenous chemotherapy within the last 14 days of life (47.8% vs. 18.4%; $P < .01$). The composite score for aggressive EOLC indicators was significantly higher for children with hematological malignancies compared with those with solid tumors ($P < .01$).

Table 2
Aggressive end-of-life care for children with hematologic malignancies compared to solid tumors

	All[a] (n = 1199)	Hematologic malignancy[a] (n = 433)	Solid tumor[a] (n = 766)	*P*-value
Last 30 days of life				
Intubation and/or mechanical ventilation	344 (28.7)	164 (37.9)	180 (23.5)	< .01
ICU admission	150 (12.5)	95 (21.9)	55 (7.2)	< .01
Cardiopulmonary resuscitation	122 (10.1)	63 (14.5)	59 (7.7)	< .01
Hemodialysis	81 (6.8)	57 (13.2)	24 (3.1)	< .01
ECMO	14 (1.2)	11 (2.5)	3 (0.4)	< .01
Tracheostomy placement	17 (1.4)	4 (0.9)	13 (1.7)	.40
Gastrostomy placement	2 (0.1)	1 (0.2)	1 (0.1)	> .99
Last 14 days of life				
Intravenous chemotherapy	348 (29.0)	207 (47.8)	141 (18.4)	< .01
Total No. intensity indicators				< .01
0	571 (47.6)	122 (28.2)	449 (58.6)	
1	367 (30.6)	150 (34.6)	217 (28.3)	
2	151 (12.6)	80 (18.5)	71 (9.3)	
3	69 (5.8)	52 (12.0)	17 (2.2)	
4	36 (3.0)	25 (5.8)	11 (1.4)	
5	5 (0.4)	4 (0.9)	1 (0.1)	

Abbreviations: ICU, intensive care unit; ECMO, extra-corporeal membrane oxygenation.

[a]Data indicate number of patients (%), unless otherwise indicated.

Table 3
Blood transfusions at end-of-life

Blood Transfusion	All[a] (n = 1199)	Hematologic malignancy[a] (n = 433)	Solid tumor[a] (n = 766)	*P*-value
Last 14 days	738 (61.7)	405 (93.5)	333 (43.5)	< .01
Last 7 days	688 (57.4)	398 (91.9)	290 (37.9)	< .01
Last 24 hours	224 (18.7)	151 (34.9)	73 (9.5)	< .01

[a]Data indicate number of patients (%), unless otherwise indicated.

Blood transfusions at EOL

Children with hematological malignancies were significantly more likely to receive a blood transfusion compared to those with solid tumors within the last 14 days of life, last 7 days of life, and even within the last 24 hours of life. Over 90% of children with hematological malignancies received a blood transfusion within the last 7 days of life, and about 35% of these children received one within the last 24 hours of life.

Factors associated with aggressive EOLC in children with hematologic malignancies

In a multivariate regression analysis, ≥ 1 aggressive EOLC indicator, ≥ 2 aggressive EOLC indicators, and CPR were associated with young age (0–4 years) in children with hematological malignancies (Table 4). For patients 0–4 years old (vs. patients 15–19 years old) the odds of 2 or more aggressive EOLC indicators was 2.3-fold higher. In particular, the odds of CPR was higher in the younger age group. Longer hospital stays were associated with a lower odds of 2 or more aggressive EOLC indicators.

Table 4
Adjusted odds ratios for receiving aggressive end-of-life care in children with hematologic malignancies

Category (Reference)	**≥ 1 aggressive indicator**		**≥ 2 aggressive indicators**		**Cardiopulmonary resuscitation**		**Intravenous chemotherapy**	
	aOR	*P*-value	aOR	*P*-value	aOR	*P*-value	aOR	*P*-value
Age, years (15–19)								
0–4	**2.11 (1.09–4.08)**	**.03**	**2.33 (1.30–4.20)**	**< .01**	**5.41 (2.20-13.28)**	**< .01**	1.06 (0.61–1.83)	.84
5–9	1.01 (0.53–1.91)	.98	1.19 (0.63–2.23)	.59	**4.21 (1.67–10.61)**	**< .01**	0.94 (0.52–1.70)	.84
10–14	1.22 (0.66–2.24)	.53	1.42 (0.79–2.56)	.24	**3.26 (1.27–8.37)**	**.01**	1.17 (0.67–2.03)	.58
Sex (Male)								
Female	0.89 (0.56–1.41)	.89	0.80 (0.51–1.23)	.31	0.74 (0.40–1.37)	.34	0.84 (0.56–1.27)	.40
Admission (Non-Urgent)								
Urgent	1.24 (0.64–2.41)	.52	1.06 (0.57–1.96)	.85	0.39 (0.13–1.21)	.10	0.75 (0.42–1.36)	.34
Length of hospital stay, days (0–29)								
30–119	1.12 (0.61–2.08)	.71	0.61 (0.34–1.09)	.10	0.59 (0.26–1.35)	.21	0.76 (0.44–1.33)	.34
120-	1.19 (0.66–2.14)	.57	**0.50 (0.28–0.88)**	**.02**	0.76 (0.35–1.63)	.48	0.65 (0.38–1.11)	.11
Hospital type (Other hospital)								
University hospital	1.47 (0.84–2.58)	.19	1.44 (0.84–2.46)	.19	1.06 (0.52–2.17)	.87	1.40 (0.85–2.32)	.19

Abbreviations: aOR, adjusted odds ratio.

Category (Reference)	≥ 1 aggressive indicator		≥ 2 aggressive indicators		Cardiopulmonary resuscitation		Intravenous chemotherapy	
Number of deaths per year in hospital (1–5)								
6–11	1.71 (0.84–3.48)	.14	1.05 (0.54–2.07)	.88	1.15 (0.46–2.89)	.76	1.68 (0.88–3.18)	.12
12–16	1.68 (0.78–3.63)	.19	0.87 (0.42–1.79)	.70	1.05 (0.39–2.82)	.93	1.73 (0.87–3.44)	.12
17-	1.24 (0.59–2.61)	.58	0.70 (0.33–1.45)	.33	0.57 (0.20–1.62)	.29	1.21 (0.61–2.40)	.58
Year (2012–2013)								
2014–2016	1.18 (0.75–1.86)	.48	1.20 (0.78–1.85)	.40	1.15 (0.64–2.08)	.65	1.23 (0.82–1.85)	.32
Abbreviations: aOR, adjusted odds ratio.								

Discussion

To our knowledge, this study is the first national survey to examine the frequency of aggressive EOLC for children with hematologic malignancies, compared to solid tumors.

We found that children with hematologic malignancies are more likely to have aggressive EOLC than those with solid tumors. Our results reveal that just over half of children (52.4%) with cancer receive at least one measure of aggressive EOLC, whereas over two-thirds of children (71.8%) with hematologic malignancies receive at least one measure of aggressive EOLC. Hematologic malignancies have a higher death rate from treatment-related complications than solid tumors,[20] so patients with hematological malignancies have a higher rate of ICU admissions due to treatment-related complications, such as acute respiratory failure and shock, compared to those with solid tumors,[21] and ICU mortality in one adult study was 39.3%.[22] Furthermore, hematologic malignancies respond better to chemotherapy, so hematologic oncologists are more likely than solid-tumor oncologists to recommend chemotherapy.[23,24] Compared to a population-based study of adults with hematologic malignancies,[6] our pediatric patients received more intravenous chemotherapy within 14 days of death than the adult patients (47.8% vs. 21%, respectively), which might reflect the higher sensitivity of pediatric hematologic malignancies even at an advanced stage. Additionally, fewer children with hematological malignancies were admitted to ICUs within 30 days of death than adults (21.9% vs. 39%, respectively), likely because of reduced morbidity. In pediatric hematologic malignancies, palliative care specialists and oncologists work together to understand the unique needs of children and develop models of concurrent palliative care.[25]

We also found that over 90% of children with hematologic malignancies received blood transfusions within 14 days of death. When compared with adults with hematologic malignancies,[26] our results revealed a much higher rate of blood transfusions (adult, 41.7%; pediatric, 93.5%) within 14 days of death, which might reflect stronger myelosuppression. At EOL, blood transfusions may be considered a way to improve quality of life.[27,28] However, providing a blood transfusion may prevent the option of dying at home or in a hospice[29] or contribute to prolonging life against the patients' own will. It is important to consider whether a transfusion is really needed and truly leads to symptom relief, and to avoid blood transfusions as a measure to sustain life.

The third important finding of our study identifies factors associated with aggressive EOLC in children with hematologic malignancies. Children under 5 years of age are more likely to receive aggressive EOLC, and CPR specifically; this is similar to reports from California.[18] While parents who choose hospice care report being influenced by their child's wishes,[30] aggressive EOLC in young children may be the result of their inability to express their wishes. Being in hospital over 120 days has a lower odds of 2 or more aggressive indicators, suggesting that for those with long anticipated hospital stays, EOL discussions may limit unnecessary intensive care.

The present study has several limitations. First, we used the national inpatient database, and did not include information on EOLC for children who died outside the hospital. Second, because we did not have the opinions of patients and families regarding EOLC, we do not know what types of EOLC patients and families want. Third, because we could not determine which children received palliative care services, we could not assess whether receiving palliative care affected the aggressive EOLC.

Conclusion

Children with hematologic malignancies are more likely to receive aggressive EOLC compared to those with solid tumors. A younger age and shorter hospital stay may be associated with aggressive EOLC in children with hematologic malignancies. The next step is to clarify how aggressive EOLC affects the children's quality of life and the grief of their bereaved families through conducting national surveys of bereaved relatives.

Abbreviations

EOL, end-of-life; EOLC, end-of-life care; DPC/PDPS, Diagnosis Procedure Combination per-diem payment system; ICU, intensive care unit; CPR, cardiopulmonary resuscitation; ECMO, extra-corporeal membrane oxygenation

Declarations

Ethics approval and consent to participate

The Institutional Review Board of the Tokyo Medical and Dental University and the National Center for Child Health and Development approved this study. The boards determined that the requirement for informed consent from patients was unnecessary because the data were anonymous.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that there is no conflict of interest.

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Author contributions

All authors made substantial contributions to the concept and design of the study. KF provided expert knowledge on the data analysis, and NY and DS performed the data analyses and developed the tables. KM, KM and YK together interpreted the results. NY wrote the first manuscript draft, all authors revised it critically, and all authors read and approved the final version.

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