Brief Report

Predictors of Late Palliative Care Referral in Children With Cancer

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Abstract

Context. Early integration of palliative care (PC) in the management of children with high-risk cancer is widely endorsed by patients, families, clinicians, and national organizations. However, optimal timing for PC consultation is not standardized, and variables that influence timing of PC integration for children with cancer remain unknown.

Objectives. To investigate associations between demographic, disease, treatment, and end-of-life attributes and timing of PC consultation for children with high-risk cancer enrolled on a PC service.

Methods. A comprehensive standardized tool was used to abstract data from the medical records of 321 patients treated at a large academic pediatric cancer center, who died between 2011 and 2015.

Results. Gender, race, ethnicity, enrollment on a Phase I protocol, number of high-acuity hospitalizations, and receipt of cardiopulmonary resuscitation were not associated with timing of PC involvement. Patients with hematologic malignancy, those who received cancer-directed therapy during the last month of life, and those with advance directives documented one week or less before death had higher odds of late PC referral (malignancy: odds ratio [OR] 3.24, $P = 0.001$; therapy: OR 4.65, $P < 0.001$; directive: OR 4.81, $P < 0.0001$). Patients who received hospice services had lower odds of late PC referral <30 days before death (OR 0.31, $P < 0.001$).

Conclusion. Hematologic malignancy, cancer-directed therapy at the end of life, and delayed documentation of advance directives are associated with late PC involvement in children who died of cancer. Identification of these variables affords opportunities to study targeted interventions to enhance access to earlier PC resources and services for children with high-risk cancer and their families. J Pain Symptom Manage 2018;55:1550–1556.

Key Words

Palliative care, palliative oncology, pediatric oncology, early integration, timing, consultation

Introduction

Cancer is the leading cause of death by disease among children in the U.S. Each year, approximately 1 in 285 children are diagnosed with cancer, and 1 in 5 children with cancer die from their disease.[1] Children with cancer and their families confront extraordinary physical, psychological, social, and spiritual difficulties throughout the illness trajectory and extending into bereavement.[2–15] Fortunately, integration of palliative care (PC) into routine cancer management has been associated with significant improvements in physical and emotional symptoms for patients,[5,16] quality of life (QOL) for children and families,[17–20] and mitigation of complicated grief for families after the death of a child.[21]

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Despite this evidence, wide discrepancies exist across different cancer centers with regards to extent and timing of PC involvement.[5,22,23] An assessment of PC services conducted by institutions affiliated with the Children's Oncology Group that was published within the last decade demonstrated that fewer than 60% of centers offered formal PC consultative services,[24] and even in centers with formal PC programs, the majority of children with relapsed, refractory, or progressive cancer were referred to PC late in their illness trajectory with a median of eight days occurring between PC consultation and death.[25,26] Although several guidelines have been published with recommendations for when to involve PC in the management of children with cancer,[27–29] little consensus and few standardized procedures exist to optimize the timing of initial PC consultation within this unique patient population.

In spite of these challenges, earlier integration of PC has been increasingly recognized over the past few years as best practice for the delivery of holistic care to children, adolescents, and young adults with cancer.[27,28,30] Formal endorsements have arisen from numerous professional organizations including the American Academy of Pediatrics, Institute of Medicine, American Society of Clinical Oncology, American Society of Pediatric Hematology/Oncology, and International Society of Paediatric Oncology. Children with cancer and their families themselves have expressed openness for PC integration as early as the time of diagnosis, recognizing its value as an additional layer of support throughout the illness journey.[31] As awareness and support increases around the concept of early PC integration for children with cancer, greater understanding of patient-specific variables that may impact timing of PC consultation for children with cancer is needed.

At present, little is known about how demographic, disease, treatment, and end-of-life (EOL) attributes are associated with timing of PC consultation for pediatric oncology patients. To address this deficit in the literature, we conducted a retrospective cohort study of deceased children with cancer enrolled on a PC service at a large academic pediatric cancer center over a four-year period. To our knowledge, this is the first study to investigate how patient-, illness-, and treatment-specific variables might impact timing of PC involvement, with the ultimate goals of identifying attributes predictive of delayed integration of PC and targeting interventions to improve access to earlier PC for these vulnerable subpopulations.

Methods

Study Design

This study was conducted at St. Jude Children's Research Hospital. The St. Jude Children's Research Hospital Institutional Review Board reviewed the study and found it exempt in the context of a retrospective analysis of a decedent cohort.

The methodology of this study has been previously described.[32] Briefly, institutional records were reviewed extensively to identify a cohort of patients with a primary cancer diagnosis, who were enrolled on a PC service at the time of their death and whose death occurred between April 1, 2011 and March 31, 2015. This time frame was selected in the context of institution-wide initiation of a comprehensive electronic medical record system on April 1, 2011, thereby facilitating a more thorough and accurate data abstraction process; secondarily, internal data from within the institution demonstrated stability regarding the frequency of requested PC consultations during this period.

A comprehensive, standardized data abstraction tool was created by pediatric palliative oncology (PPO) clinicians and researchers (E. C. K. and J. N. B.) based on a thorough review of the literature.[23,33–39] The rigorous development and the content of this standardized tool have been described.[32] The final data abstraction form encompassed 67,308 data cells, spanning demographic, disease, treatment, and end-of-life attributes as well as variables related to PC involvement.

With regards to data abstraction and auditing methodology, a team of six researchers (E. C. K., J. J., C. A. G., S. D., L. B., and L. -M. J.) independently abstracted data from the electronic medical record using the standardized tool, with subsequent additional review of paper charts for secondary supplementation. Random sampling was applied to facilitate a 10% audit of the database, with an a priori interrater reliability acceptability threshold established at 0.85. All database items met this threshold; however, two items had interrater reliability scores at precisely 0.85, so a subsequent 15% audit was performed on these items that demonstrated interrater reliability scores of 0.90 for these data.

Statistical Analysis

Logistic regression was used to determine whether demographic, disease, treatment, EOL, and PC-related characteristics of PPO patients were associated with timing of PC involvement, with and without adjustment for primary cancer diagnosis. Given previously described literature suggesting benefits of PC involvement early in the disease course,[27,28,30] the concept of "late" PC involvement was defined antithetically as PC referral occurring <30 days before death. Statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC). A two-sided significance level of $P < 0.05$ was used for all statistical tests.

Results

A total of 321 PPO patients died between April 2011 and March 2015 at the large academic cancer center represented in this study. Routine demographic characteristics are summarized in Table 1. Attributes related to disease, treatment, complications, and EOL care for this cohort have been described previously.[32] Notably, primary analysis of this cohort demonstrated that three-fourths of PPO patients had PC involvement occurring 30 days or more before death (73.5%), and the median time between first PC consultation and death was 79 days.[32]

The results of the logistic regression models exploring the relationship between PPO patient characteristics and timing of PC involvement, with and without adjustment for primary cancer diagnosis, are shown in Tables 2 and 3. Primary cancer diagnosis was significantly associated with timing of PC involvement and was controlled for in all other associations, as detailed in the following.

Gender, race, ethnicity, enrollment on a Phase I protocol, number of PICU hospitalizations, receipt of cardiopulmonary resuscitation, and status of advance directives at the time of death were not significantly associated with timing of PC involvement, with and without adjustment for primary cancer diagnosis. Cancer-directed therapy during the last month of life, hospice involvement, age at death, and time interval between advance directive documentation and death were all significantly associated with the timing of PC involvement, with and without adjustment for primary cancer diagnosis.

Table 1
Pediatric Palliative Oncology Patient Demographics ($N = 321$)

Characteristics	*n* (%)
Gender	
Male	187 (58.3)
Female	134 (41.7)
Race	
Unknown	5 (1.6)
White	217 (67.6)
Black/African American	60 (18.7)
Other	39 (12.1)
Ethnicity	
Hispanic/Latino	58 (18.1)
Non-Hispanic	263 (81.9)
Religious affiliation	
Unknown/unaffiliated	27 (8.4)
Christian/Catholic	284 (88.4)
Other	10 (3.1)
Geographic affiliation	
Northeast	17 (5.3)
Midwest	53 (16.5)
South	215 (67)
West	11 (3.4)
International	25 (7.8)

Specifically, PPO patients with a primary diagnosis of hematologic malignancy had higher odds of late PC involvement, defined by initial consult occurring less than 30 days before death (odds ratio [OR]: 3.24, 95% CI: 1.58−6.65, $P = 0.001$), as compared to those with a primary diagnoses of solid tumor (reference) or brain tumor (OR: 2.69, 95% CI: 1.40−5.17, $P = 0.003$).

Patients who were five years or younger at the time of death also had higher odds of initial PC involvement occurring less than 30 days before death, as compared to patients who were 13 years or older at the time of death, with (OR: 2.02, 95% CI: 1.06−3.82, $P = 0.032$) and without (OR: 1.94, 95% CI: 1.05−3.57, $P = 0.033$) adjustment for primary cancer diagnosis.

Similarly, patients who received cancer-directed therapy during the last month of life had higher odds of late PC involvement compared to those who did not receive cancer-directed therapy during the last month of life, with (OR: 5.52, 95% CI: 2.91−10.49, $P < 0.0001$) and without (OR: 4.65, 95% CI: 2.61−8.28, $P < 0.0001$) adjustment for primary cancer diagnosis.

In addition, patients with an advance directive in place seven days or less before death had higher odds of late PC involvement compared to those who had an advance directive in place greater than seven days before death, with (OR: 4.81, 95% CI: 2.47−9.34, $P < 0.0001$) and without (OR: 4.81, 95% CI: 2.54−9.13, $P < 0.0001$) adjustment for primary cancer diagnosis.

Conversely, patients enrolled on hospice at the time of death had lower odds of late PC involvement as compared to those not enrolled in hospice, with (OR: 0.29, 95% CI: 0.15−0.57, $P < 0.001$) and without (OR: 0.31, 95% CI: 0.17−0.56, $P < 0.001$) adjustment for primary cancer diagnosis.

Discussion

Identification of attributes predictive of late PC involvement in the care of children with cancer is a necessary first step toward development of targeted interventions to improve access to PC for all eligible children and families. To this end, this is the first study to describe how disease, illness, PC, and EOL attributes are associated with timing of PC consultation for children with cancer and their families.

Notably, a number of demographic and treatment variables did not demonstrate evidence of a statistically significant association with timing of PC consultation. Both before and after adjusting for primary cancer diagnosis, neither race nor ethnicity was associated with timing of PC or hospice involvement in the

Table 2

Logistic Regression Modeling of Days Between First Palliative Care Consult and Death as Predicted by Demographic, Disease, and Treatment Characteristics

	<30 Days From First PC Consult			
	Unadjusted		Adjusted[a]	
Characteristics	OR (95% CI)	*P*	OR (95% CI)	*P*
Demographics				
Gender				
Male	Reference		Reference	
Female	0.91 (0.55–1.50)	0.704	0.91 (0.55–1.53)	0.728
Race, $n = 316$				
White	Reference		Reference	
Black/African American	0.97 (0.51–1.86)	0.936	1.12 (0.58–2.19)	0.730
Other	0.69 (0.30–1.59)	0.385	0.62 (0.27–1.45)	0.272
Ethnicity				
Non-Hispanic	Reference		Reference	
Hispanic/Latino	0.77 (0.39–1.50)	0.439	0.72 (0.36–1.43)	0.345
Disease and treatment history				
Primary cancer diagnosis				
Solid tumor	Reference			
Brain tumor	2.69 (1.40–5.17)	**0.003**		
Leukemia/lymphoma	3.24 (1.58–6.65)	**0.001**		
Enrollment on Phase I protocol, $n = 315$				
No	Reference		Reference	
Yes	0.71 (0.42–1.19)	0.191	0.65 (0.38–1.10)	0.111
Cancer-directed therapy during LMOL, $n = 260$				
No	Reference		Reference	
Yes	4.65 (2.61–8.28)	**<0.0001**	5.52 (2.91–10.49)	**<0.0001**
PICU history				
No. of PICU hospitalizations				
0	Reference		Reference	
1	1.55 (0.87–2.78)	0.139	1.60 (0.88–2.92)	0.124
≥2	0.95 (0.51–1.79)	0.878	1.12 (0.56–2.24)	0.750
No. of PICU hospitalizations, $n = 165$[b]				
1	Reference		Reference	
2	0.76 (0.35–1.67)	0.502	0.89 (0.38–2.08)	0.792
≥3	0.43 (0.16–1.16)	0.094	0.53 (0.19–1.54)	0.247
Underwent CPR, $n = 164$[b]				
No	Reference		Reference	
Yes	2.37 (0.91–6.16)	0.078	1.77 (0.65–4.8)	0.262

OR = odds ratio; LMOL = last month of life; PICU = pediatric intensive care unit; CPR = cardiopulmonary resuscitation.
P values < 0.05 are indicated in bold text to denote statistical significance.
All models are based on the sample size of 321 unless otherwise noted; reduced sample size is due to missing data. The reference category is ≥30 days.
[a]Adjusted for primary cancer diagnosis.
[b]Based on the subgroup of patients who had one or more PICU hospitalizations.

PPO population at our large cancer center. This notable finding corroborates a single earlier study investigating the impact of race on timing of advance directives or EOL discussions in pediatric cancer patients[40] yet deviates substantially from the adult oncology literature in which race impacts access to and utilization of PC resources and services.[41] The issue of race as it relates to early integration of PC warrants extensive further exploration in the context of pediatric oncology.

These data also demonstrate that PPO patients with a primary diagnosis of hematologic malignancy have higher odds of late PC involvement as compared to children with other cancer diagnoses. Similar findings have been corroborated in the adult oncology literature, in which patients with blood cancers are less likely to have access to PC earlier in their illness course, if at all.[42,43] The rationale for these disparities ranges from perceived barriers to integration of PC with cancer-directed therapy specific to hematologic malignancy clinicians, to unique disease attributes that predispose patients to acute deterioration at the EOL with circumstances that challenge traditional hospice paradigms.[43,44] Regardless of etiology, however, the fact that certain oncology populations are more likely to receive PC than others speaks to the inherent limitations of consultative paradigms, in which primary oncologists serve as exclusive gatekeepers to access of PC services for eligible patients and families.[45] Further research is needed to explore alternative models for equitable access and provision of PC services and resources to children with high-risk cancer irrespective of primary disease type.

In addition, patients who were five years or younger at the time of death had higher odds of late PC involvement (initial consultation occurring less than

Table 3
Logistic Regression Modeling of Days Between First Palliative Care Consult and Death as Predicted by Quality of Life and End-of-Life Characteristics

	<30 Days From First PC Consult			
	Unadjusted		Adjusted[a]	
Characteristics	OR (95% CI)	*P*	OR (95% CI)	*P*
Palliative care variables				
Hospice involvement, $n = 319$				
No	Reference		Reference	
Yes	0.31 (0.17–0.56)	**<0.001**	0.29 (0.15–0.57)	**<0.001**
Age at death, yrs				
≥13	Reference		Reference	
0–5	1.94 (1.05–3.57)	**0.033**	2.02 (1.06–3.82)	**0.032**
6–12	0.90 (0.48–1.68)	0.737	0.86 (0.45–1.64)	0.651
Advance directives in place, $n = 249$				
No	Reference		Reference	
Yes	2.08 (0.68–6.31)	0.198	2.38 (0.76–7.42)	0.135
Days from advance directive to death, $n = 225$[b]				
>7	Reference		Reference	
≤7	4.81 (2.54–9.13)	**<0.0001**	4.81 (2.47–9.34)	**<0.0001**

P values < 0.05 are indicated in bold text to denote statistical significance.
All models are based on the sample size of 321 unless otherwise noted; reduced sample size is due to missing data. The reference category is ≥30 days.
[a]Adjusted for primary cancer diagnosis.
[b]Based on the subgroup of patients who had advance directives in place.

30 days before death) as compared to older patients, before and after adjusting for disease type. This phenomenon has not been described in the literature previously in the context of pediatric oncology. A recent review of community-based PC in children with life-limiting conditions identified several studies in which higher rates of hospice enrollment were seen in older children and attributed the lower utilization of hospice services in younger children to their lower likelihood to be included in decision making.[46] This finding also may speak to parental perception of the role or responsibility of "good parenting"[47,48] in the context of a younger population, although this hypothesis is grounded anecdotally without supporting empiric data. Alternatively, the illness trajectory of younger children with cancer might be unique from that of older pediatric cancer patients, resulting in later PC in the context of acute decompensation or precipitous progression events. Given the paucity of data on this younger cohort, additional studies are needed to corroborate and further explore this finding, as well as to investigate potential differences in PC involvement for verbal vs. nonverbal patients. Future work in this area may inform questions with regards to the fiduciary responsibility of clinicians who care for children with serious illness who are unable to speak for themselves.

Similarly, receipt of cancer-directed therapy during the last month of life yielded a statistically significant association with late PC involvement occurring during the last month of life. This finding is potentially concerning given the fact that children with cancer who undergo moderate- or high-intensity cancer-directed therapy frequently experience physical and psychosocial burdens associated with therapy,[2,5] and earlier PC involvement might be particularly beneficial for these patients and families. Unfortunately, some pediatric oncologists may be inclined to offer cancer-directed therapy even at the EOL in the setting of misconstruing PC as "giving up" or "abandonment."[49] In a large survey study of pediatric oncologists, more than 80% of respondents acknowledged that children with cancer tend to receive chemotherapy beyond the point at which it would be beneficial for either disease or symptomatic control, with many reportedly prescribing cancer-directed therapy solely due to parental request.[50] However, it is also important to consider recent data from Wolfe et al., which suggest that children with cancer who receive mild cancer-directed therapy during the final 12 weeks of life may experience improved psychological outcomes.[2] Further research is needed to determine whether timing of PC involvement may lessen provision of moderate- or high-intensity cancer-directed therapy at the EOL, while simultaneously allowing space for provision of lower intensity treatments that may promote psychological well-being.

Interestingly, patients with documentation of advance directives occurring less than a week before death also had higher odds of late PC involvement. Although not a causal finding, these data suggest that earlier PC involvement may play a role in earlier documentation of advance directives, corroborating data from the pediatric PC literature.[51] Ideally, this finding should be explored through rigorous prospective investigation, with an emphasis on ascertaining whether earlier PC integration yields earlier advance directive documentation with subsequent translation into decreased

incidence of aggressive interventions at the EOL, enhanced QOL, and improved provision of goal-concordant care for PPO patients and their families.

This study has a number of limitations. First, it represents the experience of a single large academic cancer center that treats patients from across the country and internationally; as such, a potential selection bias exists for higher risk patients and families seeking more aggressive therapies. Second, retrospective data abstraction is inherently flawed in the context of imperfect documentation. Although incomplete or missing data were minimal in this study, we cannot be certain that missing data occurred randomly. Third, retrospective cohort design limits our ability to make conclusions about chronology or causality. Rather, this study identifies associations that warrant future study through further prospective investigation. Despite these limitations, this study offers the first retrospective investigation of how patient-, illness-, and treatment-specific variables might impact timing of PC involvement for children who die from cancer and sets the stage for future work in this important and understudied area.

Conclusion

Patient demographics, including race and ethnicity, did not demonstrate evidence of a statistically significant association with late PC involvement for children at a large academic cancer center. However, certain disease and treatment attributes, including primary diagnosis of hematologic malignancy, receipt of cancer-directed therapy at the end of life, and delayed documentation of advance directives, were associated with late PC involvement in children with cancer. Identification of attributes predictive of late PC involvement in the care of children with cancer is a necessary first step toward development of targeted interventions to improve access to PC for all deserving children and families.

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