



The do-not-resuscitate-like (DNRL) order, a medical directive for limiting life-sustaining treatment in the end-of-life care of children with cancer: experience of major cancer center in Brazil

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Abstract

Purpose In the last few decades, interest in palliative care and advance care planning has grown in Brazil and worldwide. Empirical studies are needed to reduce therapeutic obstinacy and medical futility in the end-of-life care of children with incurable cancer. The aim of this study was to investigate the effects of do-not-resuscitate-like (DNRL) orders on the quality of end-of-life care of children with incurable solid tumors at a cancer center in Brazil.

Methods A retrospective observational cohort study of 181 pediatric patients with solid tumors followed at the Pediatric Oncology Department of the Brazilian National Cancer Institute, Rio de Janeiro, Brazil, who died due to disease progression from 2009 to 2013. Medical records were reviewed for indicators of quality of end-of-life care, including overtreatment, care planning, and care at death, in addition to documentation of the diagnosis of life-limiting illness and the presence of a DNRL order. Data were summarized using descriptive statistics. Univariate and multivariate logistic regression analyses were used to examine associations between demographics, disease, treatment, and indicators of end-of-life care with a DNRL order.

Results A documented DNRL order was associated with lower odds of dying in the intensive care unit or emergency room (80%), dying within 30 days of endotracheal tube placement (80%), or cardiopulmonary resuscitation (CPR) administration at the time of death (96%).

Conclusion Placement of DNRL orders early in the disease process is critical in reducing futile treatment in pediatric patients with incurable cancer.

Keywords Do-not-resuscitate order · Cancer · Pediatric · Solid tumor · Palliative care medicine

Introduction

Palliative care (PC), as defined by the World Health Organization (WHO), is an approach that improves the quality of life of patients with life-threatening illnesses through the prevention and relief of suffering by means of the treatment of pain and other physical, psychosocial, and spiritual problems [1]. The implementation of PC programs and their

integration early in the disease process should be a priority in developing countries [2].

Interest in PC in Brazil has grown over the last 15 years. Multidisciplinary care team members have sought to improve the quality of the PC delivered to patients and their families, and a few PC services have been implemented across the country. According to the National Academy of Palliative Care (ANCP), in 2018, there were 177 PC services in Brazil, but only 38 had a pediatric unit [3]. In the last two decades, two important end-of-life care resolutions for patients 18 years of age or older were adopted by the Federal Council of Medicine (CFM): (a) an advance directive of wishes, [4] and (b) an orthothanasia resolution, which authorizes physicians to limit or withhold life-prolonging interventions and treatments in case of emergencies in imminently dying patients with a life-limiting illness, respecting the patient's or legal guardian's wishes [5]. Nevertheless, a

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validated reference guideline for decision-making about end-of-life care of children is currently unavailable in Brazil, so parents are encouraged to be involved in the entire decision-making process [6].

When treating children and adolescents with life-limiting diseases, curative and palliative therapy measures must be balanced carefully. In near-death cases, patients may receive care from first-aid providers who are not familiar with the patient's medical history and/or the goals and wishes of the patient/family, increasing the likelihood that often unwanted life-sustaining interventions may be administered [7].

Cardiopulmonary resuscitation (CPR) is an invasive medical treatment widely used to treat patients with a potentially reversible cardiopulmonary arrest and for whom there is a reasonable possibility of therapeutic benefit. While it can be a life-saving intervention, CPR is not an effective treatment for people with a terminal illness or who are approaching the end of their natural lives.

Do-not-resuscitate (DNR) orders provide a mechanism through which resuscitation can be avoided in cases not indicated and is part of the advanced care planning carried out by shared decision-making between doctors, patients, and their family [8].

In the USA, DNR orders are well established among children with irreversible or terminal illness or complex chronic illness experiencing suffering that is refractory to care. An “allow natural death” (AND) order is a term used at some hospitals as an alternative to the more traditional DNR order [9]. Full discussion with a multidisciplinary care team, including the mandatory presence of the attending physician, is critical so that everyone understands the circumstances under which a DNR or AND order would go into effect, and the specific actions that will or will not be taken [10].

According to the European Resuscitation Council (ERC) Guidelines for Resuscitation 2015, the traditional medical-centered approach, with an emphasis on beneficence, has shifted toward a patient-centered approach with greater emphasis on non-maleficence and patient autonomy. This shift has allowed patients and their families to be involved as active partners in the end-of-life decision-making process [11].

Rellensmann and Hasan (2009) developed a strategy, in case of an emergency, to record the preferences of pediatric patients with life-limiting illness on the way to perform diagnosis and therapy, which should always be discussed in advance with the medical team. Their strategy, known as a do-not-resuscitate-like order (DNRL), is very similar to a DNR order, but in this case, it is not legally binding and was designed to provide guidance about appropriate end-of-life decisions for children with incurable disease who are nearing the end of their life [12].

In 2009, the Pediatric Oncology Department at the Brazilian National Cancer Institute (INCA) introduced an end-of-life care checklist that includes current disease status and patient/family preferences, as well as provisions for documentation in the medical record of a DNRL order. In an attempt to encourage participation of the patient/family in the care plan while respecting patient autonomy, family care conferences are held with the multidisciplinary team to provide disease prognosis, education, and support to ensure that the sharing of the information provides the maximum benefit to the patient [13].

This study aimed to investigate the effects of a DNRL order in the end-of-life care planning of children with incurable cancer at a major cancer center in Brazil.

Methods

This is a retrospective observational cohort study of 181 children and adolescents with solid tumors who died of disease progression at INCA, Rio de Janeiro, Brazil, between 2009 and 2013.

The inclusion criteria were patients aged 0–18 years with solid tumors at diagnosis, who were registered at the Pediatric Oncology Department at INCA, and were followed at the institution during treatment until death due to disease progression. Patients who died within 30 days of registration were excluded from the study.

Setting

Brazil is an upper-middle-income country with a population of 214 million inhabitants, with approximately 25% younger than 15 years [14].

INCA is a branch of the Ministry of Health for the development and coordination of integrated actions for cancer prevention and control in Brazil. The Pediatric Oncology Department at INCA is a referral center for the treatment of childhood cancer in Brazil. The multidisciplinary treatment is free of charge to all cancer patients in the country's Unified Health System, known as SUS [15]. About 250 new patients with cancer, aged 0 to 19 years old, are admitted annually. Of the 250 patients, about 180 have solid tumors. Many patients are socioeconomically underprivileged, do not have medical insurance, and are socially vulnerable.

According to Brazilian Institute of Geography and Statistics (IBGE) data, Christianity is the most frequent religion practiced in Brazil. Most Christians are either

Catholic or Evangelical, indicating that a great deal of intermarriage occurs in this country, in addition to the syncretism between Christian religions and Afro and/or indigenous ones [14, 16].

Palliative care at INCA

In 2008, a PC outpatient clinic was created, and palliative visits were provided to inpatients. An ICU was also implemented. An interdisciplinary palliative team works in all sectors of the Pediatric Oncology Department and in the pediatric emergency department. There is also a pain clinic that works with the PC team.

The advanced end-of-life care plan for children and adolescents with cancer included a structured assessment with the following documentation:

1. Consensus decision achieved at the clinical interdisciplinary meeting of the Pediatric Oncology Department that curative therapy measures were currently unavailable for the patient.
2. Diagnosis of currently incurable disease (CID) documented in the patient's medical record.
3. Family conference with the oncology attending physician and the interdisciplinary PC team. The patient's or guardian's treatment preferences were determined during a comprehensive clarification of the expected course of the disease and possible complications. The team talked about not using life-substituting measures, which artificially prolong life but also suffering, and was available to answer questions from caregivers and to interact and provide information whenever requested or necessary.

Care was individualized, always respecting the family's preferences, matching the biology with the patient's biography. The patient's involvement in the decision depended on some factors, the main one being the willingness to participate in the decisions and the level of autonomy. However, whenever possible, and the parents were comfortable, the patients were involved in their end-of-life decisions.
4. Information on the decisions were added to the medical record by the attending physician setting up the advance care plan for the patient, including the DNRL order.

The data collected were as follows: demographics (age at diagnosis and death, sex, race); disease (diagnosis and stage) and treatment (number and type of chemotherapy, cycles/regimens, time between the last chemotherapy session, and death); related characteristics; and time between

the placement of a DNRL order in the medical record and date of death.

Medical records were reviewed for indicators of quality of end-of-life care in addition to documentation of diagnosis of a currently incurable disease and the presence of DNRL order in the medical record.

The variables related to the indicators of poor quality of end-of-life care were as follows: [17, 18].

- a. **Indicators of poor quality of care planning:**
 - b. \geq One emergency room (ER) visits in the last 30 days of life;
 - c. \geq One hospital admission in the pediatric intensive care unit (PICU) in the last 30 days of life;
 - d. \geq 14 days' stay in the hospital ward or PICU in the last 30 days of life.
- b. Indicators of poor quality of treatment (overtreatment):
 - Last infusion of chemotherapy within 14 days of death;
 - Last infusion of chemotherapy less than 30 days before death;
 - Starting a new chemotherapy regimen within the last 30 days of life.
- iii. Indicators of poor quality of care at death (life-sustaining treatment):
 - Death in the ER or PICU;
 - Endotracheal intubation (ETI) in the last 30 days of life;
 - CPR prior to death.

Although these are originally considered quality indicators, [17, 18] they might not be associated with quality of life, since death in the hospital may be appropriate, when symptoms are very difficult to control or it is the patient/family preference [13].

Statistical analysis

Demographics, diseases, treatments, and indicators of end-of-life care-related characteristics were summarized using descriptive statistics. The chi-square test was used to investigate differences in these characteristics between pediatric patients, with or without a DNRL order. Univariate and multivariate logistic regression analyses were used to examine associations between demographics, diseases, treatments, and indicators of end-of-life care with a DNRL

order. Variables with a univariate analysis p -value < 0.20 were included in the multiple logistic regression model by forward-stepwise selection, and odds ratios (OR) and 95% confidence intervals (95% CI) were computed. All analyses were performed using IBM SPSS Statistics for Windows, version 21.0.

Results

Patient characteristics

The sociodemographic and clinical characteristics of patients are summarized in Table 1. Age at diagnosis ranged from 0 to 16 years (mean age: 6.7 years, median age: 5 years) and age at death ranged from 0 to 22 years (mean age: 5.8 years, median age: 5 years). The more

prevalent cancers were central nervous system (CNS) and bone tumors, and more than half of the patients (51.4%) had metastatic disease at diagnosis (Table 1).

Associations of end-of-life care indicators and DNRL order

A DNRL order was entered in the medical records of 71.3% of pediatric patients. The time from placement of the DNRL order to death was ≤ 14 days for 50.4% of the patients, 15–30 days for 16.3%, and > 30 days for 33.3%. In the current study, 30.4% patients died in the PICU or ER. The association between a documented DNRL order and indicators of poor quality of end-of-life care was statistically significant only for fewer life-sustaining treatments at death: 82.2% of patients with a signed DNRL order did not die in the PICU or ER, 82.2% were not intubated, and 97.7% did not receive CPR prior to death (Table 2).

Univariate analysis of the association between a documented DNRL order and indicators of poor quality of end-of-life care planning, treatment, and care at death showed a significant reduction in the use of physiologically futile invasive support measures. Placement of a DNRL order was significantly associated with lower odds of death in the PICU or ER (80%), ETI placement within 30 days of death (80%), and CPR administration at the time of death (96%) (Table 3).

In the multivariate analysis, death in PICU and CPR were the two explanatory variables associated with placement of a DNRL order, indicating that the risk of dying in PICU/ER and CPR prior to death was reduced by 70% and 90%, respectively, in patients with a documented DNRL order. The other variables were not associated with placement of a DNRL according to the multivariate model (Table 4).

Discussion

Following the implementation in 2009 of an end-of-life care plan in the Pediatric Oncology Department at our institution, we observed that most pediatric patients (71.3%) who died due to disease progression during the study (2009–2013) had a recorded DNRL order.

Interestingly, a study conducted at the PICU of a university hospital in Brazil revealed that healthcare providers involved in the care of children with terminal illness expressed concerns about possibly facing legal action for medical neglect. In that study, the lack of a pediatric PC service may have contributed to dysthanasia. [19].

Dysthanasia means “death with suffering,” where there is an artificial extension of life through the use of measures to replace vital functions, which occurs more frequently

Table 1 Number (%) of pediatric cancer patients by demographics, disease, and clinical stage

Variables	No. of patients (%)
Sex	
Male	98 (54.1)
Female	83 (45.9)
Ethnicity	
White	104 (57.5)
Non-white	77 (42.5)
Age at diagnosis (years)	
0–1	27 (14.9)
2–5	62 (34.3)
6–11	45 (24.9)
12–16	47 (25.9)
Age at death (years)	
0–1	6 (3.3)
2–5	58 (32.0)
6–11	45 (24.9)
12–22	72 (39.8)
Diagnosis	
Brain tumors	51 (28.2)
Bone tumors	39 (21.5)
Soft-tissue sarcomas	30 (16.6)
Neuroblastoma	26 (14.4)
Retinoblastoma	15 (8.3)
Renal tumors	10 (5.5)
Germ cell tumors	4 (2.2)
Carcinoma and other epithelial neoplasms	4 (2.2)
Liver tumors	2 (1.1)
Staging at diagnosis	
Metastatic	93 (51.4)
Non-metastatic	88 (48.6)
Total	181 (100)

Table 2 Association of indicators of poor quality of end-of-life care and placement of a DNRL order

	DNRL		<i>p</i> -value
	No	Yes	
	<i>N</i> (%)	<i>N</i> (%)	
Indicators of poor quality of care planning			
> 1 ER visits in the last 30 days of life			
No	34 (65.4)	74 (57.4)	0.320
Yes	18 (34.6)	55 (42.6)	
> 1 hospital admission in the PICU in the last 30 days of life			
No	49 (94.2)	125 (96.9)	0.400
Yes	3 (5.8)	4 (3.1)	
> 14 days admitted in the hospital ward and/or PICU in the last 30 days of life			
No	29 (55.8)	82 (63.6)	0.330
Yes	23 (44.2)	47 (36.4)	
Indicators of poor quality of treatment (overtreatment)			
Last infusion of chemotherapy within 14 days before death			
No	4 (7.7)	19 (14.7)	0.198
Yes	48 (92.3)	110 (85.3)	
Last infusion of chemotherapy less than 30 days before death			
No	34 (65.4)	98 (76.8)	0.147
Yes	18(34.6)	31(24.0)	
Starting a new chemotherapy regimen within the last 30 days of life			
No	50 (96.2)	118 (91.5)	0.354
Yes	2 (3.8)	11 (8.5)	
Indicators of poor quality of care at death			
Death in the ER or PICU			
No	20 (38.5)	106 (82.2)	<0.001
Yes	32 (61.5)	23 (17.8)	
Endotracheal intubation in the last 30 days of life			
No	26 (50.0)	106 (82.2)	<0.001
Yes	26 (50.0)	23 (17.8)	
Cardiorespiratory resuscitation before death			
No	33 (63.5)	126 (97.7)	<0.001
Yes	19 (36.5)	3 (2.3)	
Total	52 (28.7%)	129 (71.3%)	181 (100%)

DNRL order, do-not-resuscitate-like order; ER, emergency room; PICU, pediatric intensive care unit

in ICUs. DNRL is a tool that helps avoid this practice and allow orthothanasia [20].

Orthothanasia means “right death.” It is understood as the desirable death, in which the extension of life does not occur artificially, allowing the natural course of an incurable disease to take place, providing patients with dignity and relief from suffering in all dimensions (physical, psychological, social, and spiritual) [21].

The term euthanasia (literally, “good death”) means death without pain [22]. Conceptually, it is understood as an intervention to shorten life, to alleviate or avoid suffering for patients with an incurable disease, and it is not a legally accepted measure in Brazil [20].

In contrast, clinicians’ decisions in the current study were not guided by legal concerns but rather were designed to provide excellent control of pain and other symptoms in patients who were nearing the end of life, especially patients with diseases for which there are currently no therapeutic options. In the current study, a documented DNRL order was correlated with better care in nearly all indicators of quality of end-of-life, and was significantly associated with a reduction in futile medical treatment.

Similarly, a study conducted in the ICU of a tertiary hospital in Brazil showed that implementation of a PC program was associated with increased DNR order placement and a trend toward reduced ICU utilization during hospitalizations

Table 3 Univariate analysis of indicators of poor quality of end-of-life care and placement of DNRL order

	OR	CI 95%	<i>p</i> -value
Poor quality indicators of care planning			
> 1 ER visits in the last 30 days of life	1.4	0.7–2.7	0.321
> 1 hospital admission in the PICU in the last 30 days of life	0.5	0.1–2.6	0.407
> 14 days admitted in the hospital ward and/or PICU in the last 30 days of life	0.7	0.4–1.4	0.331
Indicators of poor quality of treatment (overtreatment)			
Last infusion of chemotherapy within 14 days before death	0.5	0.2–1.5	0.206
Last infusion of chemotherapy less than 30 days before death	1.7	0.8–3.4	0.149
Starting a new chemotherapy regimen within the last 30 days of life	2.3	0.5–10.9	0.282
Indicators of poor quality of care at death (intensive supportive care)			
Death in the PICU or ER	0.2	0.07–0.3	<0.001
Endotracheal intubation in the last 30 days of life	0.2	0.1–0.4	<0.001
Cardiorespiratory resuscitation before death	0.04	0.01–0.2	<0.001

DNRL order, do-not-resuscitate-like order; PICU, pediatric intensive care unit; ER, emergency room; OR, odds ratio; CI, confidence interval

Table 4 Explanatory variables associated with placement of a DNRL order

Independent variables	Adjusted OR	CI 95%	<i>p</i> -value
Death in PICU or ER	0.3	(0.1–0.7)	0.004
Cardiorespiratory resuscitation before death	0.1	(0.03–0.4)	0.001

DNRL order, do-not-resuscitate-like order; PICU, pediatric intensive care unit; ER, emergency room; OR, odds ratio; CI, confidence interval

of end-of-life patients, indicating that the placement of a DNR order was associated with lower odds of dying in the ICU [23].

Supporting the importance of documenting care planning, Osinski et al. (2017) recommended discussing DNR orders for adult cancer patients through shared decision-making to prevent medical futility [24]. In contrast, in a cohort of pediatric oncology patients, ongoing medical interventions were continued after the placement of a DNR order, with the exception of chemotherapy [25].

In a study of pediatric cancer patients, Kaye et al. (2018) showed that lack of advance care planning or advance directives such as DNR orders was directly associated with late PC involvement [26]. That study reinforces our findings and highlights the importance of introducing DNRL as early as possible.

A retrospective study of pediatric oncology patients conducted at a US pediatric cancer center reviewed the medical records of children who died of cancer. The study reported that of the 122 patients who died in the hospital, 44.3% died in the PICU. Patients with late PC involvement occurring less than 30 days before death had higher odds of dying in the ICU over a home or hospice setting [27]. In that study, an advance directive order was in place at the time of death

in 70.1% of pediatric palliative oncology patients, and of those advance directives, 25.8% were placed ≤ 7 days before death [27]. In contrast, in the current study, 50.4% of DNRL orders were placed < 14 days before death and 30.4% died in the PICU or ER.

It is noteworthy that measures to extend life were used less often. Sharing the decision and listening to caregivers are very important to ensure that families feel well supported, and should be considered indicators of end-of-life quality. Tomlinson et al. studied the use of chemotherapy versus exclusive PC in children with cancer, and showed how particular the perception of quality of care is [28].

The hope that cancer can be cured, even if not based on a reasonable possibility, can be a factor for parents' desire to give chemotherapy at the end of life. The perception of parents can be different from that of health professionals. Further studies are needed to show the relationship between the avoidance of futile treatment and perceived quality of end-of-life care.

Conclusion

The placement of a DNRL order early in the disease process, preferably as early as diagnosis of life-limiting illness has been made, is critical to improve patients' end-of-life experiences. During conferences with the multidisciplinary team, family members and/or patients should be informed about the possibility of limiting invasive support measures and withholding life-sustaining treatments. It is important that all palliative measures are included in the advance care plan to provide excellent control of suffering in all dimensions. Placement of a DNRL order as early as possible in the medical record of a larger number

of children with incurable cancer is critical for reducing futile medical treatment. Clarification of advance care planning and support for families and patients early in the disease process is vital for improving the quality of end-of-life care.

Author contribution All authors contributed to the study conception, design, data acquisition, interpretation and analysis, and manuscript writing. All authors read and approved the final manuscript.

Data availability Not applicable.

Code availability Not applicable.

Declarations

Ethics approval The study was approved by the institutional Research Ethics Committee under number CAAE 45998915.5.0000.5274.

Consent to participate According to retrospective study design, consent to participate was not necessary.

Consent for publication Not applicable.

Conflict of interest The authors declare no competing interests.

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