Original Article

Intensity of Cancer Care Near the End of Life at a Tertiary Care Cancer Center in Jordan

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Abstract

Context. Chemotherapy use in the last month of life is an indicator of poor quality of end-of-life care.

Objectives. We assessed the frequency of chemotherapy use at the end of life at our comprehensive cancer center in Jordan and identified the factors associated with chemotherapy use.

Methods. We conducted a retrospective chart review to examine the use of chemotherapy in the last 30 days and 14 days of life in consecutive adult patients with cancer seen at King Hussein Cancer Center (KHCC) who died between January 1, 2010, and December 31, 2012. We collected data on patient and disease characteristics, palliative care referral, and end-of-life care outcome indicators.

Results. Among the 1714 decedents, 310 (18.1%) had chemotherapy use in the last 30 days and 142 (8.3%) in the last 14 days of life. Over half (910; 53.1%) had a palliative care referral. Chemotherapy use in the last 30 and 14 days of life were associated with younger age (odds ratio [OR] 0.99/yr, $P = 0.01$, and OR 0.99/yr, $P = 0.01$, respectively) and hematological malignances (OR 1.98, $P < 0.001$, and OR 2.85, $P < 0.001$, respectively). Palliative care referral was significantly associated with decreased use of chemotherapy in the last 30 (OR 0.30, $P < 0.001$) and 14 (OR 0.15, $P < 0.001$) days of life.

Conclusions. A sizable minority of patients with cancer at KHCC received chemotherapy at the end of life. Younger patients and those with hematological malignancies were more likely to receive chemotherapy, whereas those referred to palliative care were significantly less likely to receive chemotherapy at the end of life. J Pain Symptom Manage 2019;57:1106–1113.

Key Words

Drug therapy, neoplasms, palliative care, quality of health care, terminal care

Introduction

The emergence of new anticancer therapeutics with an increasing number of indications,[1,2] coupled with the strong influence of mass media and pharmaceutical marketing campaigns, has resulted in enormous pressure on health care providers, health care payers, and policy makers to provide cancer treatments even for patients with far advanced disease. A review of studies from several countries showed that many patients with cancer would choose to receive aggressive chemotherapy with major adverse effects for a small possibility of benefit despite their physician's recommendations.[3] Use of chemotherapy at end of life became even more complex with the introduction of molecular targeting and immune-checkpoint agents, which are considered more tolerable than other types of chemotherapy associated with fewer significant toxicities and side effects in general and durable response in some individuals.[4]

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Earle et al. suggested that the use of chemotherapy near the end of life is a major quality-of-care issue. Studies have shown that palliative chemotherapy in the last months of life is associated with more aggressive end-of-life care, such as intensive care unit (ICU) admissions.[5–9] In 2012, an American Society of Clinical Oncology expert panel identified chemotherapy use among patients for whom there was no evidence of clinical value as the most widespread, wasteful, and unnecessary practice in oncology.[10] A recent study showed that the use of chemotherapy for patients with advanced cancer in the last week of life was significantly associated with higher estimated costs of end-of-life care.[11] This is a particularly important issue for low- or middle-income countries.

Jordan is a middle-income country in which more than 6000 new cancer cases are diagnosed annually,[12] and this number is expected to rise. Despite the availability of advanced diagnostics and therapeutics in Jordan, more than 40% of patients with cancer present in advanced stages.[12] To date, the frequency of chemotherapy use near the end of life in Jordan is not known. A better understanding of the frequency and predictors of chemotherapy use would provide valuable information for clinicians, administrators, and policy makers to identify ways to improve the quality of end-of-life care. Therefore, we assessed the frequency of and factors associated with chemotherapy use at the end of life at our comprehensive cancer center.

Patients and Methods

Study Design

The study was conducted as a retrospective chart review. All patients ≥18 years of age who died between January 1, 2010, and December 31, 2012, at King Hussein Cancer Center (KHCC) or at home while under the care of KHCC were included. Only patients with advanced stage (stage 3 and 4), advanced brain tumors, or advanced hematological malignancies were included. Patients with cause of death other than cancer were excluded.

Ethical Considerations

The study protocol was approved by the KHCC Institutional Review Board. Because this was a retrospective chart review, a waiver of informed consent was obtained.

Study Setting

KHCC is a not-for-profit organization and the largest tertiary cancer center in Jordan. Over 3000 new cancer cases are treated at KHCC per year, accounting for approximately 50% of all cancer cases in Jordan.[13] The center follows regularly updated international practice guidelines, and all cases are discussed in disease-specific multidisciplinary meetings using the latest international standards. KHCC has also built the largest comprehensive palliative and home care program in the country.[13]

Data Collection

Data were extracted from archived electronic medical records. We recorded patients' basic demographics, including age and sex, in addition to tumor characteristics including tumor type, date of diagnosis, and tumor stage at death.

We recorded all patients who received any chemotherapy during their lifetime and determined if they received chemotherapy in the last 30 and last 14 days of life, whether it was the start of a new chemotherapy regimen or continued existing chemotherapy. This is a modification from the original Earle criteria,[14] but consistent with other published reports.[15,16] We recorded the number of days between the last administration of chemotherapy and death. We used the term chemotherapy to denote all cytotoxic chemotherapeutic, targeted, and immunotherapeutic agents.

We also collected outcome indicators for end-of-life care in the last 30 and 14 days of life, including the number of emergency room (ER) visits, hospital admissions, and ICU admissions, as well as length of hospital stay. Palliative care referral was also recorded for all patients.

Statistical Analysis

Patients' characteristics were presented as counts and percentages or mean and range depending on data type. Median time from the last dose of chemotherapy to death and the median time from palliative referral to death were calculated. Rate of chemotherapy use at end of life was calculated by dividing the number of patients who received chemotherapy within 14 or 30 days of death by the total number of patients in the same period. Comparison between patients who and did not receive chemotherapy in the last 30 and 14 days of life was held according to demographics and disease information; Chi-square test or Fisher's exact test was used to compare categorical data. Multivariate analysis, including all significant factors ($P \leq 0.05$) identified in univariate analysis, was carried out by logistic regression model. Probability was modeled on receiving chemotherapy and assessing the effect of entered factors, such as age, primary tumor, stage at death and palliative care referral, and other end-of-life outcome indictors. A significance criterion of $P < 0.05$ was used in the analysis. Cancer survival was presented by Kaplan Meier curves.

Comparison in survival times was performed using log-rank test among the following risk factor levels. All analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC).

Results

Patient Characteristics

General characteristics of the 1714 patients included in the analysis are reported in Table 1. The most common malignancy types were gastrointestinal (n = 391, 22.8%) and hematological (n = 317, 18.5%). Over half (910; 53.1%) of all patients were referred to palliative care services, with a median interval of 35 days (interquartile range 11−105 days) before death (Table 1).

Patients Who Received Chemotherapy

Most (1283; 74.9%) patients received chemotherapy during their lifetime. The rate of chemotherapy use within 30 days of death was 18.1% (n = 310) and within 14 days was 8.3% (n = 142). Most patients who received chemotherapy within 30 and 14 days of death had hematological malignances (103/310 [33.2%] and 65/143 [45.5%], respectively) (Table 2). The rate of chemotherapy use in the last 30 days of life decreased from 18.9% in 2010 to 14.5% in 2012 and from 9.7% in 2010 to 6.0% in 2012 for the last 14 days of life (Table 2). The median time from the last dose of chemotherapy to death was 72.5 days (interquartile range 31−177 days).

Table 1
Patient Characteristics (N = 1714)

Characteristic	n (%)
Gender	
Male	907 (52.9)
Female	807 (47.1)
Age (yrs)	
Mean (SD)	53 (15.1)
Median (IQR)	54 (42.4−64.5)
Primary tumor	
Breast	272 (15.9)
Brain	92 (5.4)
Gastrointestinal	391 (22.8)
Genitourinary	102 (6.0)
Gynecological	93 (5.4)
Head and neck	93 (5.4)
Hematological malignancies	317 (18.5)
Lung cancer	205 (12.0)
Skin and soft tissue	99 (5.8)
Others	50 (2.9)
Chemotherapy[a]	
Yes	1283 (74.9)
No	431 (25.1)
Palliative referral	
Yes	910 (53.1)
No	804 (46.9)
Place of death	
Home	35 (2.0)
Hospital	1679 (98.0)
Year of death	
2010	587 (34.2)
2011	541 (31.6)
2012	586 (34.2)
Days between last dose of chemotherapy to death, median (IQR)	72.5 (31−177)
Days between palliative referral to death, median (IQR)	35 (11−105)

SD = standard deviation; IQR = interquartile range.
[a]Refers to lifetime chemotherapy; chemotherapy was defined as any systemic cancer therapy, including chemotherapy, targeted therapy, immunotherapy, or hormonal therapy.

Outcome Indicator of Aggressive Care at End of Life

The data provided in Table 3 indicate that patients who received chemotherapy in the last 30 days of life had a lower quality of end-of-life care compared with those who did not receive chemotherapy within this time. Specifically, chemotherapy use in the last 30 days of life was associated with at least one ICU admission (P < 0.001), two or more ER visits (P = 0.002), and two or more hospital admissions (P = 0.03; Table 3).

Factors Associated With Chemotherapy Use

In our cohort, use of chemotherapy within both the last 30 and last 14 days of life was significantly associated with age (both P < 0.001), tumor type (both P < 0.001), palliative care referral (both P < 0.001), and year of death (P = 0.01 and P = 0.04, respectively) in univariate analysis (Table 2). As shown in Figure 1, factors such as age, primary tumor, stage, and palliative care referral were associated with survival time from last chemotherapy dose.

Multivariate regression analysis demonstrated age, tumor type, palliative care referral, and year of death to be independently associated with chemotherapy administration within the last 30 and 14 days of life. Younger patients were more likely to receive chemotherapy in the last 30 (OR 0.99/yr, P = 0.01) and 14 days of life (OR 0.99/yr, P = 0.01). Patients with hematological malignancies were also more likely to receive chemotherapy in the last 30 (OR 1.98, P < 0.001) and 14 days of life (OR 2.85, P < 0.001). In contrast, patients seen by palliative care were less likely to receive chemotherapy in the last 30 (OR 0.30, P < 0.001) and 14 (OR 0.15, P < 0.001) days of life (Table 4).

Discussion

Our study is the first study in Jordan to evaluate the aggressiveness of care and use of chemotherapy for patients with cancer at the end of life. A sizable minority of patients with cancer at KHCC received chemotherapy at the end of life. Younger patients and those with hematological malignancies were more likely to

Table 2
Chemotherapy Within 30 and 14 Days of Death—Univariate Analysis ($N = 1714$)

Variable	Value	No Chemotherapy Within Last 30 days of Life, 1404 (81.9%)	Chemotherapy Within Last 30 days of Life, 310 (18.1%)	*P*-value[a]	No Chemotherapy Within Last 14 days of Life, 1571 (91.7%)	Chemotherapy Within Last 14 days of Life, 143 (8.34%)	*P*-value[a]
Gender	Male	740 (52.7%)	167 (53.9%)	0.71	824 (52.5%)	83 (58.0%)	0.20
	Female	664 (47.3%)	143 (46.1%)		747 (47.5%)	60 (42.0%)	
Age (yrs)	Mean (SD)	53.8 (15.3)	49.6 (14.3)	<0.001	53.5 (15.2)	47.8 (14.7)	<0.001
	Median (IQR)	55.2 (43.5, 65.3)	50.7 (39.5, 60.9)		54.5 (42.9, 65.0)	48.8 (37.3, 60.5)	
Primary tumor	Breast	227 (16.2%)	45 (14.5%)	<0.001	259 (16.5%)	13 (9.1%)	<0.001
	CNS	87 (6.2%)	5 (1.6%)		91 (5.8%)	1 (0.7%)	
	Gastrointestinal	323 (23.0%)	68 (21.9%)		369 (23.5%)	22 (15.4%)	
	Genitourinary	94 (6.7%)	8 (2.6%)		98 (6.2%)	4 (2.8%)	
	Gynecological	85 (6.1%)	8 (2.6%)		89 (5.7%)	4 (2.8%)	
	Head and neck	84 (6.0%)	9 (2.9%)		92 (5.9%)	1 (0.7%)	
	Hematological	214 (15.2%)	103 (33.2%)		252 (16.0%)	65 (45.5%)	
	Lung cancer	164 (11.7%)	41 (13.2%)		183 (11.6%)	22 (15.4%)	
	Others	44 (3.1%)	6 (1.9%)		47 (3.0%)	3 (2.1%)	
	Skin/soft tissue	82 (5.8%)	17 (5.5%)		91 (5.8%)	8 (5.6%)	
Palliative care referral	Yes	824 (58.7%)	86 (27.7%)	<0.001	890 (56.7%)	20 (14.0%)	<0.001
	No	580 (41.3%)	224 (72.3%)		681 (43.3%)	123 (86.0%)	
Years	2010 ($n = 587$)	476 (81.1%)	111 (18.9%)	0.01	530 (90.3%)	57 (9.7%)	0.04
	2011 ($n = 541$)	427 (78.9%)	114 (21.1%)		490 (90.6%)	51 (9.4%)	
	2012 ($n = 586$)	501 (85.5%)	85 (14.5%)		551 (94.0%)	35 (6.0%)	

CNS = central nervous system; SD = standard deviation; IQR = interquartile range.
[a]*P*-values calculated by Chi-square test, except for primary tumor (Monte Carlo estimation).

receive chemotherapy at the end of life, whereas patients referred to palliative care were significantly less likely to do so.

The use of chemotherapy near death is a major indicator of intensive care at end of life.[14,17] Our study reported the rate of use of chemotherapy as 18.1% in the last 30 days and 8.34% in the last 14 days of life. Our frequencies of chemotherapy use at the end of life fall within the range reported in other countries with a fairly large sample size compared with similar studies in the literature (Table 5).

In our study, patients with hematological malignancies were the most frequent group to receive chemotherapy within 30 days (33.2%) and 14 days before death (45.5%), which is similar to findings reported by Hui et al.[15] and Rautakorpi et al.[18] This may be due to the nature of hematological malignancies, which are more sensitive to chemotherapy. A qualitative study reported that many hematologic oncologists found it difficult to recognize the end-of-life phase for their patients because of continued possibility of cure even in advance diseases and the often "rapid pace of decline near death" for these patients.[34] In the same study, participants expressed limited palliative care involvement in patients with hematologic malignancies,[34] consistent with other retrospective studies.[15,35]

In our cohort, use of chemotherapy at end of life was significantly associated with younger age ($P < 0.001$). Of importance, Jordan has a relatively young population, with a median age of 22.5 years. According to the National Cancer Registry, the median age at diagnosis was 56 years.[36] The observation that younger patients were more likely to receive treatment at the end of life is consistent with other studies.[27,37] Lee et al. also found that older patients (>65 years) and patients with less responsive tumors tend to receive less chemotherapy.[30]

Table 3
Indicators of Aggressive Cancer Care ($N = 1714$)

Variable	No Chemotherapy Within Last 30 days of Life	Chemotherapy Within Last 30 days of Life	*P*-value	No Chemotherapy Within Last 14 days of Life	Chemotherapy Within Last 14 days of Life	*P*-value
N (%)	1404 (81.9%)	310 (18.1%)		1571 (91.7%)	143 (8.34%)	
ER visit	1282 (91.3%)	291 (93.9%)	0.14	1437 (91.5%)	136 (95.1%)	0.13
Two or more number of ER visits	787 (56.1%)	204 (65.8%)	0.002	904 (57.5%)	87 (60.8%)	0.44
Hospital admission	1289 (91.8%)	294 (94.8%)	0.07	1446 (92.0%)	137 (95.8%)	0.11
Two or more number of hospital admissions	416 (29.6%)	111 (35.8%)	0.03	481 (30.6%)	46 (32.2%)	0.70
Days stayed in hospital ≥14	600 (42.7%)	135 (43.5%)	0.79	681 (43.3%)	54 (37.8%)	0.20
ICU admissions	658 (46.9%)	213 (68.7%)	<0.001	757 (48.2%)	114 (79.7%)	<0.001

ER = emergency room; ICU = intensive care unit.
P-values calculated by Chi-square test.

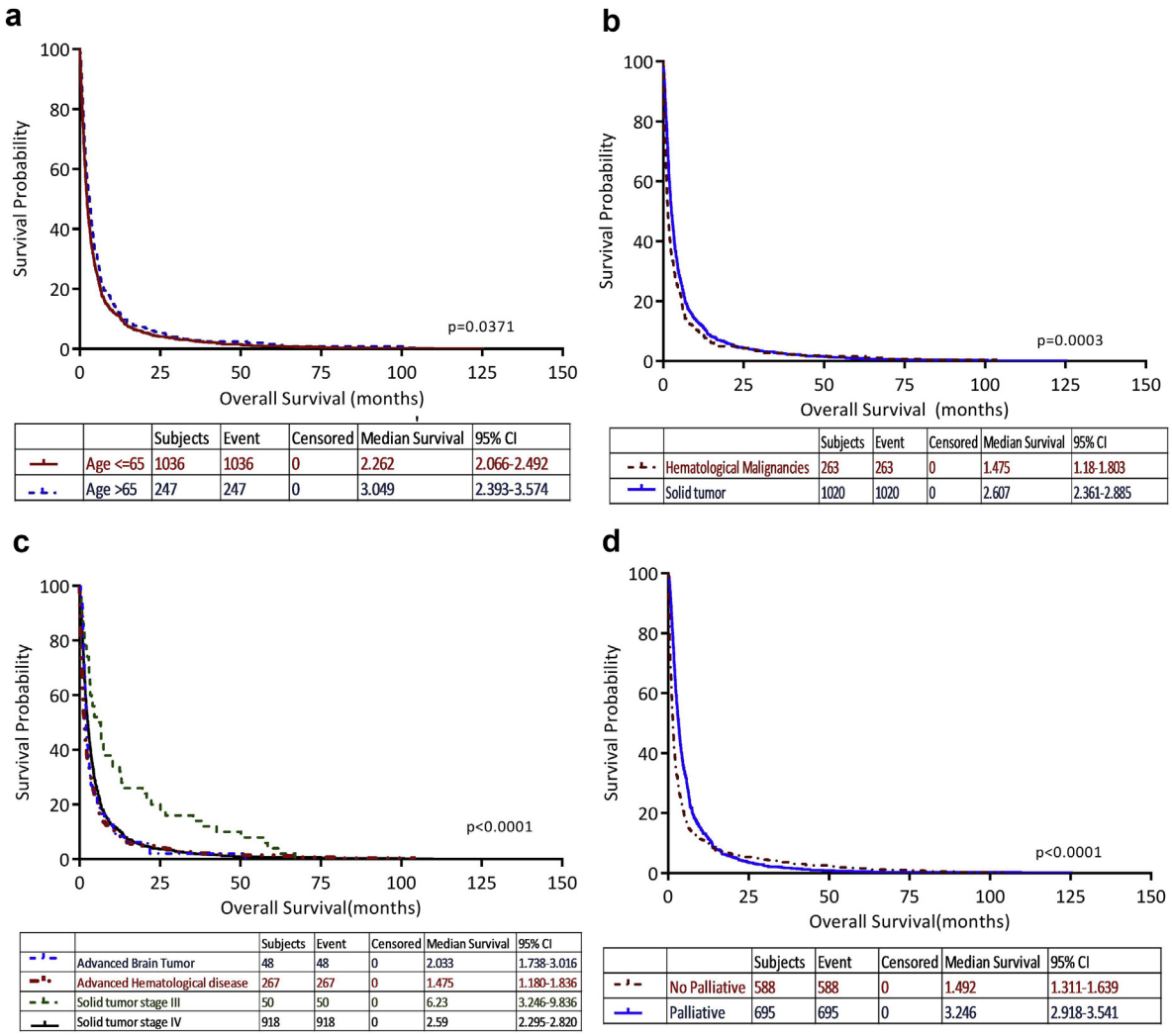

Fig. 1. Kaplan Meier curves for last chemo use date to death by a) age groups >60/<60, b) tumor type, c) clinical stage and d) palliative referral.

In our study, patients seen by palliative care were significantly less likely to receive chemotherapy within the last 30 and 14 days of life. Similarly, Magarotto et al. found that integration of supportive and palliative care services was associated with a reduction of chemotherapy use from 19% in 2006 to 14% in 2009 for patients in their last 30 days of life.[23] The lower rates of chemotherapy among patients seen by palliative care may be related to patients either stopping chemotherapy before palliative care referral or after further encounters with the palliative care team. Multiple studies have suggested that early referral to palliative care is an important factor to reduce the use of aggressive therapy at end of life[17,23,38] by facilitating understanding of the illness and effective end-of-life planning, effectively managing symptoms, and offering psychosocial support and spiritual care.[39]

Table 4

Factors Associated With Chemotherapy Use in the Last 30 and 14 Days of Life—Multivariate Analysis

	Chemotherapy Within 30 Days		Chemotherapy Within 14 Days	
Effect	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age	0.990 (0.983–0.997)	0.01	0.987 (0.977–0.997)	0.01
Primary tumor (hematological vs. solid tumor)	1.979 (1.482–2.643)	<0.001	2.847 (1.975–4.103)	<0.001
Palliative care referral (yes vs. no)	0.297 (0.225–0.392)	<0.001	0.147 (0.090–0.240)	<0.001
Year (2010 vs. 2012)	1.456 (1.061–1.999)	0.02	1.698 (1.089–2.646)	0.02
Year (2011 vs. 2012)	1.742 (1.268–2.392)	<0.001	1.804 (1.151–2.828)	0.01

OR = odds ratio; CI = confidence interval.

Table 5
Rate of Chemotherapy Use at End of Life Around the World

First Author	Title	Year	Country	*N*	30 days	14 days
Rautakorpi[18]	End-of-life chemotherapy use at a Finnish university hospital: a retrospective cohort study	2017	Finland	11,250		2.1
Barbera[19]	Indicators of poor quality end-of-life cancer care in Ontario	2006	Canada	21,323		4.2
Keam[20]	Aggressiveness of cancer care near the end of life in Korea	2008	Korea	298		5.7
Adam[21]	Chemotherapy near the end of life: a retrospective single-centre analysis of patients' charts	2014	Switzerland	119	11.7	7.6
Goncalves[22]	Use of chemotherapy at the end of life in a Portuguese oncology center	2008	Portugal	1064	13	3
Magarotto[23]	Reduced use of chemotherapy at the end of life in an integrated care model of oncology and palliative care	2011	Italy	361	By year: 2006 19 2007 20 2008 16 2009 14	
Kao[24]	Use of chemotherapy at end of life in oncology patients	2009	Australia	747	18	8
Hui[25]	Targeted agent use in cancer patients at the end of life	2013	USA	816	27	
Abdelrazeq & Shamieh	Intensity of cancer care near the end of life at a tertiary care cancer center in Jordan	2018	Jordan	1714	18.1	8.3
Martoni[26]	Cancer chemotherapy near the end of life: The time has come to set guidelines for its appropriate use	2007	Italy	793	22.7	
Nappa[1]	Palliative chemotherapy during the last month of life	2011	Sweden	374	23	
Goksu[27]	Use of chemotherapy at the end of life in Turkey	2014	Turkey	373	23.9	10.5
Earle[28]	Trends in the aggressiveness of cancer care near the end of life	2004	USA	28,777		15.7
Braga[29]	The aggressiveness of cancer care in the last three months of life: a retrospective single-centre analysis	2007	Portugal	319	37	21
Lee[30]	Trends in receiving chemotherapy for advanced cancer patients at the end of life	2015	Korea	2345	By year: 2000 22 2005 37 2010 56	
Low[31]	Chemotherapy use at the end of life in Uganda	2017	Uganda	595	45.4	
Mohammad[32]	End-of-life palliative chemotherapy: Where do we stand?	2015	Saudi Arabia	420	55.6	22.6
Ortiz[33]	Chemotherapy at the end of life: up until when?	2012	Spain	303	55.6	33.8

We observed a decrease in the rate of chemotherapy use within 30 days and 14 days of death between 2010 and 2012 (overall percent change 23.3% and 38.1%, respectively). We hypothesize that this may be related to enhanced recognition of palliative care at KHCC and the establishment of the Palliative Care department in 2011 during which KHCC revised the criteria for palliative care referral and increased awareness and advocacy for palliative care among staff, patients, and families.[13]

Chemotherapy use in the last 30 days of life was also associated with at least one ICU admission, two or more ER visits, and two or more hospital admissions in our study. This is not surprising given that patients who choose to receive chemotherapy at the end of life may also have a stronger preference for life-sustaining measures. Furthermore, chemotherapy related adverse effects are more likely to occur in frail patients, requiring more acute care resource use. Based on data from the Coping with Cancer Study, chemotherapy use was associated with an increased risk of ICU death, mechanical ventilation, and cardiopulmonary resuscitation.[8] Similarly, Wu C-C reported that palliative chemotherapy was significantly associated with more than one ER visit, more than one ICU admission, and endotracheal intubation at end-of-life.[5] In addition, Saito et al. found that ICU admissions, ER visits, and deaths in the hospital were more frequent in patients receiving chemotherapy with a notable increase in frequency as death approach.[7] Many other factors may influence the use of chemotherapy near end of life. Patients' understanding of their survival may impact how much more treatment they would like to seek[40]; however, accurate prediction of survival is always challenging. A recent meta-analysis of 13 studies indicated that oncologists consistently overestimate prognosis by ≥30%.[41] A recent multisite study reported that patients with advanced cancer

receiving palliative care in Jordan were eight times more likely to have an inaccurate perception of curability of their cancer than patients from the U.S.[42] In addition, physicians may recommend injudicious use of chemotherapy to avoid difficult discussion with the patient and the family about death and end-of-life care.[43] Some oncologists were highly reluctant to stop chemotherapy even if they were told the patient has a performance status of 4 and is expected to live one month.[44]

This study has several limitations. This study was carried out in a single institution. Of note, our institution is the only tertiary referral center in Jordan, serving over 50% of all cancer patients in the country. Our findings may not be generalizable to other smaller general hospitals in the nation. Recurrent disease was not included in our definition of advanced cancer, which may have affected our interpretation. Another limitation is that we did not make a distinction between patients who started new chemotherapy regimen and those who continued existing chemotherapy. This is partly because every treatment cycle is preceded by an oncology visit to weigh the risks and benefits and to decide if patients should continue or not. Owing to the retrospective nature of this study, we were not able to collect data on some important variables that may affect the decision on chemotherapy use, such as performance status, patients' goals of care, oncologists' prediction of patient survival, and sociocultural factors including income, religion and educational level. In addition, we did not collect data on the exact nature of anticancer treatment (i.e., chemotherapy, targeted therapy, immunotherapy, or hormonal therapy), chemotherapy line, or response to last line. This should be addressed in future studies; moreover, future directions may include evaluating oncologists', patients', and families' attitudes toward the use of chemotherapy at end of life[28] and cost-related issues.[11,45]

Conclusion

At our tertiary care cancer center, 18.1% and 8.3% of patients received chemotherapy in the last 30 and 14 days of life, respectively. Referral to palliative care was associated with less intensive treatment and improved quality of care at end of life. Further studies are needed to examine how to increase palliative care referral and improve quality of end-of-life care for patients with cancer.

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