

Psychological factors at early stage of treatment as predictors of receiving chemotherapy at the end of life

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Abstract

Introduction: Administration of chemotherapy in the last 14 days of life is a widely recognized indicator of poor end-of-life (EOL) care. The current study aimed to investigate predictors of this outcome, focusing on patients' self-reported psychological symptoms.

Methods and Materials: This is a secondary analysis of a randomized controlled trial that examined the efficacy of early palliative care integrated with standard oncology practice in patients with metastatic non-small cell lung cancer (NSCLC). We analyzed associations between receipt of chemotherapy within 14 days of death and demographic, clinical, and quality-of-life variables in the 125 patients who received chemotherapy in the course of their illness and died during the 50-month follow-up.

Results: Twenty-five patients (20%) received chemotherapy within the last 14 days of their life. Among demographic and clinical variables, only route of chemotherapy was significantly associated with receipt of chemotherapy within 14 days of death (oral 34.1% vs. intravenous (IV) 12.3%, $p < 0.05$). In the subsample of participants who received IV chemotherapy as their last regimen, greater anxiety and depression and lower quality of life in emotional, social, and existential domains were associated with greater likelihood of receiving chemotherapy at the EOL. These associations were not observed in patients who received oral chemotherapy as their last regimen.

Conclusion: Anxiety, depression, and worse psychological quality of life at early stage of treatment may be associated with the receipt of IV chemotherapy at the EOL. Further research is needed to examine how these factors might influence decision-making about the discontinuation of chemotherapy at the EOL.

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Introduction

Aggressive medical care for patients with advanced cancers at the end of life (EOL) is associated with higher cost and worse quality of life in both patients and their caregivers [1,2], while conferring questionable benefit for prolonging life [3]. Recent data from Wright and colleagues showed that administering chemotherapy to terminally ill cancer patients in the last months of life was later associated with an increased risk of aggressive medical care at the EOL, including cardiopulmonary resuscitation, mechanical ventilation, and dying in an intensive care unit [4]. The administration of chemotherapy at the EOL has become a major focus of quality care initiatives. The American Society of Clinical Oncology recognizes it as an indicator of poor quality care and listed decreasing the administration of chemotherapy at the EOL as one of the top five ways to improve the quality and decrease the cost of cancer care [5]. Nevertheless, recent large-scale studies in the USA and Canada report that the rate of chemotherapy administration within the last 2 weeks of patients' life has been increasing for the past 15 years, comprising 3.7% to 16% of cancer patients [6,7].

Stopping treatment at the EOL may be one of the most affect-laden decisions in medicine. However, there has been little research on how emotions or other psychological factors might influence the discontinuation of chemotherapy. Previous work has focused on patient variables that are easy to collect from administrative databases such as demographic (e.g., male gender and younger age) [6,8], cancer type (e.g., hematologic cancer or breast cancer, compared with lung cancer) [7,8], care settings (e.g., teaching hospital) [6], and healthcare system (e.g., Medicare, compared with Canadian health system in Ontario) [9]. Although informative, those variables are mostly factors that cannot be modified and, consequently, offer limited opportunities to improve the quality of EOL care. Prospective research involving potentially modifiable targets have been mainly limited to palliative care service involvement [10] and the presence and quality of EOL discussions [11–14].

Outside of medicine, emotions have been shown to influence decision-making across different situations and settings [15,16]. It is likely that emotions and psychological factors also influence medical decisions, particularly those with emotional salience. Prior research has shown

that patients' psychological well-being is associated with their preferences for decision-making [17] as well as their understanding of their prognosis [18], which is a strong predictor of EOL care wishes [17]. Additionally, although not specific to chemotherapy at the EOL, we previously reported that higher levels of anxiety were associated with aggressive EOL care in 50 patients with metastatic lung cancer [19].

If psychological factors do, in fact, predict the receipt of chemotherapy within 14 days of death, they may be key targets for improving EOL care because they can be addressed with interventions. To investigate the relationship between patients' psychological factors and the receipt of chemotherapy at the EOL, we conducted a secondary analysis of data from a clinical trial of early palliative care for patients with metastatic non-small cell lung cancer (NSCLC). We explored the associations of patient-reported anxiety, depression, and quality of life with the receipt of chemotherapy close to death. We hypothesized that worse anxiety, depression, and quality of life would later predict the receipt of chemotherapy at EOL, specifically within 14 days before death.

Methods

Sample

This secondary analysis utilized data from a randomized controlled trial that examined the efficacy of early palliative care integrated with standard oncology practice. Full details of the trial were published elsewhere [20]. In brief, between June 7, 2006, and July 15, 2009, 151 ambulatory patients within 8 weeks of diagnosis of metastatic NSCLC participated in the trial. Eligible participants had a diagnosis of metastatic NSCLC, an Eastern Cooperative Oncology Group performance status of 0 to 2, and the ability to read and respond to questions in English. Patients who were already receiving care from the palliative care service were excluded. The Dana-Farber/Partners Cancer Care institutional review board approved the study protocol, and all participants provided written informed consent.

The analytic sample for this study included only participants who (1) received any chemotherapy during the course of their illness, (2) deceased at time of current analysis, and (3) had available data on the date of last chemotherapy administration prior to death. Because past studies have shown that the route of last chemotherapy regimen (oral targeted therapies versus other systemic intravenous (IV) chemotherapies) has significant impact on receipt of chemotherapy at EOL [8], we first conducted our analyses with whole sample and then divided them into those who received oral chemotherapy alone and those who received IV chemotherapy (including combination with oral chemotherapy) as the last regimen.

Measures

Trained research staff collected electronic health record data concerning baseline and subsequent clinical information of each participant, including the receipt of chemotherapy (IV or oral) within 14 days of death. At study enrollment, participants provided demographic information and completed the following instruments.

Functional Assessment of Cancer Therapy-Lung

The Functional Assessment of Cancer Therapy-Lung (FACT-L) consists of two scales: the FACT-general, a 27-item questionnaire that comprises four subscales assessing physical, social, emotional, and functional well-being during the past week; and the Lung Cancer Subscale, a seven-item questionnaire that evaluates specific symptoms related to lung cancer. Items in both scales ask about the frequency of experiencing symptoms, thoughts, or feelings and have five potential responses that are anchored. Higher scores indicate better quality of life [21].

McGill Quality of Life Questionnaire

The McGill Quality of Life Questionnaire (MQOL) was designed to assess quality of life in patients with life-threatening illnesses [22]. The questionnaire consists of 16 items with an 11-point scale (0–10). It includes four subscales, namely physical, psychological, existential, and support domains. In the original trial, the physical domain of the MQOL was not included because it was felt to be similar to the physical well-being subscale of the FACT-L.

Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) is a 14-item self-report questionnaire that contains two subscales measuring anxiety and depression symptoms in the past week. Scores for each subscale range from 0 (no distress) to 21 (maximum distress) [23].

Patient Health Questionnaire-9

The Patient Health Questionnaire-9 (PHQ-9) is a nine-item instrument that assesses depressive symptoms [24]. It can be scored continuously for a measure of symptom levels and categorically for presumed diagnosis of major depression syndrome. The participants were categorized as having major depressive syndrome if they answered 'more than half the days' to one of two of core depressive symptoms, and also if they endorsed five or more symptoms in total.

Statistical analysis

Descriptive summaries of demographic and clinical variables were compiled. We examined demographic, clinical, and psychosocial differences between those who did and

did not receive chemotherapy within the last 14 days of life. Chi-square and Fisher's exact tests were used for categorical variables and Wilcoxon's rank-sum tests for continuous variables. The small sample size of the subgroups prohibited us from conducting multivariate analyses. We considered all *p*-values at the two-sided alpha level of 0.05 to be statistically significant. SPSS version 21.0 (IBM, Armonk, NY, USA) was used.

Results

Patient characteristics

By 50-month follow-up, 144 of the 151 participants had died. Among them, nine participants never received chemotherapy, six withdrew from the study, and four patients lacked medical record data on last chemotherapy administration, resulting in 125 patients in the final analysis. Table 1 summarizes the characteristics of the analytic sample. The mean survival length of the participants was 11.4 months. Eighty-one patients received IV chemotherapy as their last regimen, and 44 patients received oral chemotherapy as their last regimen.

Administration of any chemotherapy at the EOL

Among the whole sample, 25 out of 125 participants (20.0%) received chemotherapy within the last 14 days of life. Participants who received oral chemotherapy alone as their last regimen were more likely to have last administration of chemotherapy within the last 14 days of life, compared with patients who received IV chemotherapy as the last regimen (34.1% vs. 12.3%; $p < 0.01$) (Table 2). We did not find associations between receipt of chemotherapy at the EOL and psychological factors, as well as demographic, clinical, and quality of life variables.

Factors associated with administration of IV chemotherapy at the EOL

In the subsample of 81 participants who received IV chemotherapy as their last regimen, greater anxiety (HADS-anxiety) and presence of major depressive syndrome (PHQ-9) were associated with greater likelihood of receiving IV chemotherapy in the last 14 days of life (Table 3). While there was no significant association with the total FACT score, worse scores on its emotional well-being subscale were associated with the receipt of chemotherapy within 14 days of death. Worse scores on one of the MQOL domains (support) were also significantly associated with the receipt of chemotherapy within 14 days of death. However, there was no association with the psychological and existential domains of the MQOL. Whether having children or not, treatment allocation (integrated early palliative care or treatment as usual), number of lines of chemotherapy, and number of use of mental health service were not significantly different between the two groups.

Table 1. Characteristics of participants

Characteristics	<i>n</i>	%
Demographic		
Age	M = 64.5	SD = 9.2
Sex		
Female	62	49.6
Race		
White	122	97.6
Black	2	1.6
Asian	1	0.8
Ethnicity		
Hispanic/Latino	2	1.6
Marital status		
Married	75	60
Single/divorced/widowed	50	40
Having children		
Yes	24	19.2
No	101	80.8
Clinical (baseline)		
Cancer stage at baseline		
IIIB	5	4
IV	120	96
ECOG performance status at baseline		
0	46	36.8
1	67	53.6
2	12	9.6
Brain metastasis	33	26.4
Smoker at diagnosis	31	24.8
Group assignment		
Standard care	66	53
Integrated early palliative care	59	47
Clinical course		
Survival months	11.4	SD = 9.2
Number of line of chemotherapy		
1	46	36.8
2	35	28.0
3	23	18.4
4 or more	21	16.8
Route of last chemotherapy		
Oral	44	35.2
Intravenous	81	64.8

ECOG, Eastern Cooperative Oncology Group; M, mean; SD, standard deviation.

Factors associated with administration of oral chemotherapy at the EOL

In the subsample of 44 participants who received oral chemotherapy as their last regimen, psychological factors were not significantly associated with the receipt of chemotherapy within 14 days of death. The only variable that has a significant association was sex, with men being more likely than women to receive oral chemotherapy at the EOL (52.6% vs. 20.0%; $p < 0.05$) (Table 4).

Discussion

These data suggest that psychological factors may be associated with the receipt of chemotherapy close to death. However, an association was only found with patients who had IV chemotherapy as their last regimen. Higher

Table 2. Predictors of any chemotherapy receipt within 14 days of life ($n = 125$)

Variables	Chemotherapy within 14 days (n/median)		Wilcoxon's W			
	No	Yes	p	χ^2	W	SE
Demographic						
Age	65.5	64.0	0.63		1496.5	161.8
Gender						
Female	51	11	0.66	0.39		
Male	49	14				
Marital status						
Married	60	15	1.00	0.01		
Single, divorced, or bereaved	40	10				
Clinical						
Route of last chemotherapy*						
Oral	29	15	<0.01	8.43		
IV (including combination of IV/oral)	71	10				
Patient reported outcomes						
FACT						
Total	73.0	79.0	0.74		1508.5	160.5
Physical well-being	22.0	21.0	0.93		1560.0	161.5
Social well-being	22.0	22.0	0.53		1674.0	159.3
Emotional well-being	16.0	15.0	0.30		1396.5	160.9
Functional well-being	15.0	15.0	0.60		1478.0	160.4
Lung cancer scale	19.0	20.0	0.96		1583.5	161.5
MQOL						
Total	74.0	72.0	0.84		1541.5	161.9
Psychological	11.5	12.0	0.20		1784.0	161.7
Existential	44.0	46.0	0.90		1554.0	161.9
Support	18.0	16.0	0.07		1289.0	157.2
HADS						
HADS – anxiety	5.0	7.0	0.43		1689.5	159.9
HADS – depression	4.0	5.0	0.37		1704.5	159.6
PHQ-9						
PHQ-9 total score	5.00	6.00	0.30		1741.5	161.6
Major depressive syndrome						
Yes	14	5	0.53	0.56		
No	86	20				
Suicide thoughts						
Yes	13	3	1.00	0.84		
Not at all	86	22				

FACT, Functional Assessment of Cancer Therapy; HADS, Hospital Anxiety and Depression Scale; MQOL, McGill Quality of Life Scale; PHQ, Patient Health Questionnaire; SE, standard error; IV, intravenous.

* $p < 0.05$.

levels of anxiety, the presence of major depressive syndrome, worse emotional well-being, and greater existential distress were all significantly associated with the receipt of IV chemotherapy within 14 days of death. While not all psychological variables had significant associations, such as the psychological domain of the MQOL and level of depressive symptoms on the PHQ-9 and HADS, a relationship between psychological distress and receipt of IV chemotherapy at the EOL was found across four separate instruments. This is even more impressive when considering that very few of the other variables were found to have associations (receiving IV versus oral

Table 3. Predictors of IV chemotherapy receipt within the last 14 days of life ($n = 81$)

Variables	Chemotherapy within 14 days (n/median)		Wilcoxon's W			
	No	Yes	p	χ^2	W	SE
Demographic						
Age	66.0	64.0	0.47		359.5	69.6
Gender						
Female	31	6	0.50	0.94		
Male	40	4				
Marital status						
Married	44	6	1.00	0.01		
Single, divorced, or bereaved	27	4				
Patient reported outcomes						
FACT						
Total	74.5	65	0.15		248.0	64.8
Physical well-being	22.0	21.0	0.37		347.5	69.4
Social well-being	22.0	21.5	0.91		402.0	68.4
Emotional well-being *	17.0	12.0	0.03		258.5	68.6
Functional well-being	16.0	11.5	0.26		328.0	68.6
Lung cancer scale	20.0	17.0	0.14		306.5	69.4
MQOL						
Total	74.0	65.5	0.051		234.0	65.6
Psychological	11.0	14.5	0.14		513.0	69.5
Existential	44.0	32.5	0.10		296.0	69.6
Support *	18.0	14.5	0.02		246.0	67.3
HADS						
HADS – anxiety *	5.0	10.5	0.05		545.5	69.3
HADS – depression	4.0	8.0	0.06		542.0	69.2
PHQ-9						
PHQ-9 total score	5.00	9.50	0.08		531.5	69.4
Major depressive syndrome*						
Yes	6	4	0.02	8.06		
No	65	6				
Suicide thoughts						
Yes	8	2	0.60	0.62		
Not at all	63	8				

FACT, Functional Assessment of Cancer Therapy; HADS, Hospital Anxiety and Depression Scale; MQOL, McGill Quality of Life Scale; PHQ, Patient Health Questionnaire; SE, standard error.

* $p < 0.05$.

chemotherapy as final route and sex for patients who received oral chemotherapy as their final regimen). These findings support our previous report of psychological distress being associated with aggressive EOL care in another sample of patients with metastatic NSCLC [19].

Psychological distress might be related to the receipt of chemotherapy through two possible mechanisms. First, psychological distress could impact patients' preferences for chemotherapy at the EOL. Patients with heightened psychological distress may be less likely to tolerate stress of not receiving chemotherapy. In-depth interviews with patients with advanced cancer [25] suggested that patients often consider chemotherapy as a coping method to enhance their sense of 'living in the present' to shift their attention away from the fear of death. For those patients, 'chemotherapy-free periods' may actually be more

Table 4. Predictors of oral chemotherapy receipt within the last 14 days of life (*n* = 44)

Variables	Chemotherapy within 14 days (n/median)		<i>p</i>	χ^2	Wilcoxon's	
	No	Yes			<i>W</i>	SE
Demographic						
Age	65.0	67.0	0.81		328.0	40.3
Gender*						
Female	20	5	0.03	5.12		
Male	9	10				
Marital status						
Married	16	9	1.00	0.09		
Single, divorced, or bereaved	13	6				
Patient reported outcomes						
FACT						
Total	69.0	80.0	0.35		384.0	41.5
Physical well-being	22.0	22.0	0.55		361.5	40.3
Social well-being	22.0	22.0	0.38		372.5	39.7
Emotional well-being	15.0	15.0	0.22		386.5	40.2
Functional well-being	14.0	16.0	0.73		351.5	40.3
Lung cancer scale	19.0	21.0	0.29		380.5	40.2
MQOL						
Total	74.0	80.0	0.38		381.5	41.5
Psychological	14.0	12.0	0.93		334.0	40.3
Existential	41.0	50.0	0.15		395.0	40.3
Support	17.0	18.0	0.95		340.0	39.4
HADS						
HADS – anxiety	5.0	4.0	0.74		317.0	39.1
HADS – depression	5.0	4.0	0.63		311.0	39.0
PHQ-9						
PHQ-9 total score	6.00	6.00	0.67		320.5	40.1
Major depressive syndrome						
Yes	8	1	0.14	2.66		
No	21	14				
Suicide thoughts						
Yes	5	1	0.40	1.02		
Not at all	23	14				

Adjusted: controlling for assignment for integrated early palliative care.

ECOG, Eastern Cooperative Oncology Group; FACT, Functional Assessment of Cancer Therapy; FACT, Functional Assessment of Cancer Therapy; HADS, Hospital Anxiety and Depression Scale; MQOL, McGill Quality of Life Scale; PHQ, Patient Health Questionnaire; SE, standard error.

**p* < 0.05.

stressful than periods when they are receiving chemotherapy, despite serious side effects. Additionally, higher levels of psychological distress are known to impair understanding of medical information [26], and this could subsequently affect patients' preferences and decision-making. Nevertheless, little support for this mechanism exists in the literature. Depression in patients with chronic illnesses has been shown to be associated with preferences for less aggressive care at the EOL [27–29]. One study of patients with advanced cancer found no associations between anxiety disorders and EOL care preferences [30].

Psychological distress might also lead to greater likelihood of receiving chemotherapy at the EOL by impacting communication between patients and oncologists. From

the patients' perspective, psychological distress generally increases behavioral disengagement and avoidance, which are known associated factors of aggressive care in the EOL [31,32]. On the other side, clinicians have been found to change their communication style according to patients' anxiety levels [33]. Oncologists tend to avoid patients' expressions of negative affect during clinical encounters [34]. When patients express negative emotions, physicians move away from emotional topics by blocking, postponing, or switching the topics [35], which could result in putting off sensitive topics such as discussions of stopping chemotherapy. Patients with life-threatening illness are known to take a passive, physician-driven decision-making style at this vulnerable period in life [36]; thus, patients and physicians may mutually reinforce attitudes of continuing chemotherapy as usual [37].

Similar to prior studies, patients receiving IV chemotherapy as their last regimen were less likely to receive chemotherapy at the EOL compared with patients receiving oral chemotherapy. Our observations that oral chemotherapies were continued closer to death and did not have significant associations with psychological factors suggest that the decision-making processes for their discontinuation may differ from that of IV chemotherapy. Further support of a difference may be that only IV and not oral chemotherapies were found to be stopped earlier in patients receiving early palliative care in the trial [10]. With their ease of administration and relatively milder toxicities, continuing oral chemotherapy may be considered to have fewer downsides, and decisions to discontinue them as death approaches may not have the same sense of urgency.

While the assessment of psychological factors earlier in the course of illness could be seen as a weakness of this study, it may actually be a strength. Analyses that examine predictors of EOL outcomes at time points defined retrospectively from death have more bias than those that examine factors prospectively from diagnosis [38]. Assessing psychological factors within 8 weeks of diagnosis may seem too early to influence EOL decisions, but selecting later time points that are clinically equivalent across patients is challenging. This is especially true in a population that has a short median survival and varying time course for deterioration and death. There is not a clear and discrete 'beginning' of the EOL after a terminal diagnosis. Prospectively, when should psychological factors be assessed? Moreover, oncologists describe EOL conversations as a process over time and not a one-time issue. Starting EOL discussions earlier in the course of illness is one of the few modifiable predictors of lower rates of chemotherapy administration at the very end of life [12,39].

Although this may be the first study to explore a potential association between psychological distress and the receipt of chemotherapy at the EOL, it has several

limitations. First, it is a post hoc analysis of a clinical trial that was not designed to investigate associations between patient-reported outcomes and the administration of chemotherapy at the EOL. Many important variables, such as patients' coping styles and treatment preferences, were not collected. Second, the sample size is relatively small, which did not allow multivariate analyses to adjust for possible confounders. Third, longitudinal repeated assessments are needed to determine the relationships over time. Fourth, significant effects may be due to the repeated use of tests of significance. Fifth, advances in the treatment of NSCLC have been made since this study was conducted, and it may not be entirely representative of current oncology practices. Finally, the sample only comprised patients who participated in a randomized clinical trial of early palliative care in a single institution, which, along with the little racial diversity, limits the generalizability of the results.

Despite these limitations, we believe our findings highlight the importance of assessing psychological distress in patients with metastatic cancer early in their care. This

may be particularly relevant to the new American College of Surgeons Commission on Cancer standard that requires the implementation of screening programs for psychosocial distress [40]. If psychological distress truly influences the receipt of chemotherapy at the EOL, screening may also represent an opportunity to improve EOL care. Screening can identify patients who may be at risk for receiving chemotherapy at the EOL and potentially decrease that risk by addressing and treating the distress.

Although our findings are exploratory and no definitive conclusions can be drawn, they clearly warrant further studies of psychological factors as predictors of the receipt of chemotherapy at the EOL. Additionally, to identify the underlying mechanisms for associations, future research should include assessments of patients' EOL care preferences, the quality of communication between patients and clinicians, and clinicians' own judgments. While more work needs to be performed, increased attention to psychological distress in patients with metastatic cancers may have far-reaching implications for EOL care.

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