Processes of Discontinuing Chemotherapy for Metastatic Non–Small-Cell Lung Cancer at the End of Life

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Abstract

Purpose: Administration of chemotherapy close to death is widely recognized as poor-quality care. Prior research has focused on predictors and outcomes of chemotherapy administration at the end of life. This study describes processes of chemotherapy discontinuation and examines their relationships with timing before death, hospice referral, and hospital death.

Patients and Methods: We reviewed health records of a prospective cohort of 151 patients with newly diagnosed metastatic non–small-cell lung cancer who participated in a trial of early palliative care. Chemotherapy treatments during final regimen were qualitatively analyzed to identify categories of discontinuation processes. We then quantitatively compared predictors and outcomes of the process categories.

Results: A total of 144 patients died, with 81 and 48 receiving intravenous (IV) and oral chemotherapies as their final regimen,

respectively. Five processes were identified for IV chemotherapy: definitive decisions (19.7%), deferred decisions or breaks (22.2%), disruptions for radiation therapy (22.2%), disruptions resulting from hospitalization (27.2%), and no decisions (8.6%). The five processes occurred at significantly different times before death and, except for definitive decisions, ultimate decisions for no further chemotherapy and referral to hospice were often made months later. Among patients receiving oral chemotherapy, 83.3% (40 of 48) were switched from IV to oral delivery as their final regimen, sometimes concurrent with or even after hospice referral.

Conclusion: Date of last chemotherapy is not a proxy for when a decision to stop treatment is made. Patients with metastatic non–small-cell lung cancer stop their final chemotherapy regimen via different processes, which significantly vary in time before death and subsequent end-of-life care.

Introduction

Patients, their families, and oncologists recognize the administration of chemotherapy near death as aggressive and poor-quality care.¹ At the end of life (EOL), not only may chemotherapy be futile, but it may also be harmful because of toxicities, avoidable hospitalization, interference with EOL care planning and hospice, and increased risk of dying in an intensive care unit.²⁻⁷ Both the American Society of Clinical Oncology Quality Oncology Practice Initiative and the National Safety Forum include the discontinuation of chemotherapy within 2 weeks before death as a quality indicator of poor EOL care.^{8,9} However, rates have been slowly rising over the last decade, and 5% to 22% of all patients with advanced cancer receive chemotherapy within 2 weeks of death.^{2-4,10-18}

Previous research on chemotherapy administration at EOL has primarily focused on predictors and outcomes. Although these studies have helped to identify the scope of the problem, few have examined when and how oncologists discontinue chemotherapy, including how the timing influences patient outcomes. Examining the process of how physicians discontinue chemotherapy is critical for identifying modifiable factors to improve physician performance and patient outcomes. Moreover, prior investigators have predominantly analyzed administrative data, which lack the granularity to study this aspect of discontinuing chemotherapy.

The goal of our study was to examine how chemotherapy for metastatic non–small-cell lung cancer (NSCLC) is discontinued at EOL. We sought to identify the processes of chemotherapy discontinuation in a sample of patients from a randomized trial of early palliative care (EPC), using mixed qualitative and quantitative methodologies. Additionally, we explored associations between these discontinuation processes and outcomes, including timing before death, use of hospice, and terminal hospitalization.

Patients and Methods

Sample

We analyzed the 151 patients with metastatic NSCLC who were enrolled onto a randomized trial of EPC between June 7, 2006, to July 15, 2009. The original trial has been described in detail elsewhere.¹⁹ Participants were within 8 weeks of diagnosis and had a good performance status (Eastern Cooperative Oncology Group [ECOG] 0 to 2). Those enrolled were randomly assigned at a 1:1 ratio to receive standard oncology care or EPC integrated with their cancer care. The trial was approved by the Dana-Farber/Harvard Cancer Center Institutional Review Board. The analytic sample included patients who had died by January 1, 2013, and had EOL care data

available for analysis. Because prior research has shown that oral chemotherapy may be continued closer to death than intravenous (IV) chemotherapy,²⁰⁻²³ we analyzed these routes of last chemotherapy administration separately.

Data Collection

Data were extracted from the trial database and collected through electronic health record (EHR) review. Two physicians (W.F.P., K.I.) reviewed oncologists' notes for all trial participants, including ambulatory visits, inpatient admission notes, and discharge summaries. We searched the EHR for oncologists' documentation of the following: chemotherapy breaks or holidays (ie, holding chemotherapy for indeterminate time with intention to consider reinitiation of chemotherapy later; dose delays were excluded), initial discussion of chemotherapy discontinuation as a treatment option, and final decisions to discontinue chemotherapy altogether.

Predictors. Predictors were as follows: age at trial enrollment, sex, marital status, race, baseline ECOG performance status, and assignment arm (standard care *v* EPC).

Outcomes. Outcomes were as follows: days between last chemotherapy and death, hospice referral (yes *v* no), days in hospice, and terminal hospitalization (yes *v* no; defined as death in hospital, in emergency room, or within 24 hours of transfer to inpatient hospice).

Statistical Analyses

Initially, two physicians explored the sequence of events and actions involved in chemotherapy discontinuation for 10 patients, from initiation of final chemotherapy regimen to death. Categories of processes of chemotherapy discontinuation were identified and refined. Ten additional patient cases were independently coded by each physician to ensure that all processes were captured by the categories. Subsequently, the two physicians independently coded the same 38 patient cases (approximately 25% of sample) in NVivo software (version 10; QSR International, Melbourne, Australia), achieving excellent reliability ($\kappa = 0.74$); one physician (W.F.P.) then coded the remaining patient cases.

Descriptive statistics were compiled separately for final regimens of IV and oral chemotherapies. Differences between IV and oral chemotherapies and associations of the categories of processes with predictors and outcomes were analyzed. We used the *t* test, analysis of variance, and Wilcoxon rank sum test to analyze continuous variables and the χ^2 test for categorical variables. We used multivariable methods to examine associations between the categories of processes and outcomes, adjusting for any significant covariates at $P < .10$. Linear regression models were used for continuous variables, and the Mantel-Haenszel test for conditional independence was used for binary outcomes. Analyses were conducted with SPSS software (version 21; SPSS, Chicago, IL), with a two-sided significance level of .05.

Table 1. Patient Demographic and Clinical Characteristics

Characteristic	Final Chemotherapy Route				P
	IV (n = 81)		Oral (n = 48)		
	No.	%	No.	%	
Age, years					.82
Mean		64.1		64.5	
SD		9.0		9.01	
Female sex	36	44.4	28	58.3	.13
Married	50	61.7	27	56.3	.54
White race	79	97.5	47	97.9	.54
ECOG performance status					.90
0	30	37.0	17	35.4	
1	43	53.1	25	52.0	
2	8	10.0	6	12.5	
Randomly assigned to early palliative care	36	44.4	27	56.3	.24
Lines of chemotherapy					.004
Median		2		2.5	
Range		1-9		1-5	
Survival, months					.02
Median		7.1		10.0	
Range		0.2-36.7		0.5-35.6	
Interval between last chemotherapy and death, days					.13
Median		55		34.0	
Range		3-548		0-732	
Chemotherapy within 14 days of death	8	9.9	18	37.5	.05

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IV, intravenous; SD, standard deviation.

Results

At the time of this analysis, 144 of 151 patients had died; 81 patients received IV chemotherapy as their last regimen, 48 received oral chemotherapy as their last regimen, nine received no chemotherapy, and six were excluded because of transfer of care or lack of EOL data. Characteristics of the patient sample are summarized in Table 1. Patients who received oral chemotherapy as their last regimen lived significantly longer and received more lines of chemotherapy.

Discontinuation of IV Chemotherapy

The median time between the last chemotherapy infusion and death was 55 days (range, 3 to 548 days). However, almost one quarter of patients in the sample had no documented decision to discontinue IV chemotherapy altogether (n = 20 of 81). Among those with documented final decisions, the median time from the decision to the patient's death was only 20 days (range, 1 to 140 days).

Oncologists documented offering the option of stopping IV chemotherapy altogether in 75.6% patients (n = 62 of 81) before their death. The following EHR excerpt from an oncologist's note is a typical example of this documentation: "We discussed options at this point including switching chemo reg-

Table 2. Processes of Discontinuing Chemotherapy

Process	Proportion of Patients (n = 81)		Description	EHR Excerpt
	No.	%		
Definitive decision	16	19.7	Final chemotherapy was followed by documented discussion about permanently stopping chemotherapy	"Worsening performance status with pressure ulcer, falls at home, and generalized weakness. We discussed goals of care and the concern that more chemo could hurt him rather than help him at this point given his declining performance status. He is very much on board with focusing on symptom control and we will initiate hospice services at home."
Deferred decision (break)	18	22.2	Documentation of discussion about explicitly discontinuing chemotherapy, with plan to re-evaluate and consider further treatment	"We discussed whether to continue chemotherapy for 40 minutes. Her disease remains stable after an initial response, but she is having fatigue, anemia, and also has this dizziness which could be from chemo. We agreed that it makes sense to go on a holiday from chemotherapy. We can restage in 2 months and, if stable, hopefully continue the chemo-break through the holiday season. If her dizziness resolves and her disease grows again in the future, we could consider [specific chemotherapy regimen]."
Disruption because of radiation treatment	18	22.2	Chemotherapy held for initiation of radiation therapy for brain or bone metastases and hemoptysis, and documentation of intent for potential chemotherapy treatment after completing radiation therapy	"Given that she will be starting radiation, we will hold chemo today. Will return after radiation for consideration of further chemotherapy."
Disruption because of hospitalization	22	27.2	Patient hospitalized before next scheduled infusion, and chemotherapy was never restarted	"Continued therapy directed at her cancer, which was the principal challenge for her, now appeared to offer her very little in terms of quality or quantity of life and with some reluctance her devoted husband agreed to a do not resuscitate/do not intubate . . . status and comfort measures only."
No decision	7	8.6	Patient died before receiving scheduled chemotherapy, and there was no documentation of stopping chemotherapy	"She is rarely leaving the house, is not letting family help, and is perseverating about her funeral. . . . She is doing well physically. Labs are adequate for therapy today and will start chemotherapy today."

Abbreviation: EHR, electronic health record.

* Patient received chemotherapy that day and died 6 days later.

imens versus best supportive care." The first time a discussion was documented, the result was stopping chemotherapy altogether in almost all cases (n = 57 [91.9%] of 62).

Processes of Discontinuing IV Chemotherapy

Five distinct processes of discontinuing chemotherapy were identified. Table 2 provides definitions and EHR excerpts. The processes are qualitatively described in this section, and Table 3 summarizes the rates, times before death, and other outcomes. The processes differed significantly in time before death, rate of chemotherapy within 14 days of death, hospice referral, days in hospice, death in the hospital, and eventual final decision for no further chemotherapy.

Definitive discussion. Poor performance status was typically cited as the primary reason for stopping, and oncologists often told patients that further chemotherapy would likely be harmful. These discussions occurred within two visits after computed tomography scans revealed cancer progression for most patients. Hospice services were always part of definitive discussions. When performance status was cited, regardless of process, the text described a lower level of functioning than implied by the documented ECOG performance status.

Deferred decision (break). At some point in their treatment, 27 (33.3%) of 81 patients took breaks, or chemotherapy holidays, from their chemotherapy with a plan to re-evaluate chemother-

apy at a later date. Two thirds of breaks (n = 18) ultimately resulted in no further chemotherapy. These discussions also usually occurred within two visits of a computed tomography scan demonstrating cancer progression, and the primary reasons cited were poor performance status, toxicities, and inability to tolerate chemotherapy. Hospice services were raised as part of the final decision discussions, but not during discussions about initiating breaks. Among those with a final decision, the median number of days from discontinuation to final decision was 128 (range, 42 to 539 days).

Treatment disruption for radiation therapy. In contrast to chemotherapy breaks, this process occurred when there was disease progression associated with severe pain or life-threatening consequences (eg, seizures or fatal bleeds). Chemotherapy was stopped to initiate radiation therapy to treat brain or bone metastases or hemoptysis. Among those who had a final decision, the median number of days between last chemotherapy and final decision was 42 (range, 21 to 185 days).

Treatment disruption because of hospitalization. Planned chemotherapy was disrupted by acute hospitalizations that seemed unexpected. Admissions were primarily for pain and symptom management, followed by pneumonia. Admission notes focused on the medical reason for the hospitalization and almost never mentioned chemotherapy plans. However, clinicians occasionally documented consultation with palliative care for

Table 3. Predictors and Outcomes of Different Processes of IV Chemotherapy Discontinuation

Characteristic	Break		Definitive Discussion		Disruption Because of Radiotherapy		Disruption Because of Hospitalization		Not Discontinued		P
	No.	%	No.	%	No.	%	No.	%	No.	%	
Total	18	22.2	16	19.7	18	22.2	22	27.2	7	8.6	
Predictors											
Age, years											.09
Mean		67.6		65.5		62.6		61.0		65.3	
SD		8.9		10.6		7.6		10.2		10.0	
Female sex	9	50.0	6	37.5	11	61.1	7	31.8	4	57.1	.26
Married	9	50.0	12	75.0	15	83.3	11	50.0	3	42.9	.09
White race	18	100.0	16	100.0	18	100.0	20	90.9	7	100.0	.24
Baseline ECOG											.26
0	7	38.9	5	31.3	7	38.9	8	36.4	3	42.9	
1	8	44.4	11	68.8	7	38.9	14	63.6	3	42.9	
2	3	16.7	0	0.0	4	22.2	0	0.0	1	14.3	
Lines of chemotherapy											.30
Median		1		2		1		1.5		2	
Random assignment											.03
Standard care	5	11.1	9	20.0	11	24.4	17	37.8	3	6.7	
Early palliative care	13	36.1	7	19.4	7	19.4	5	13.8	4	11.1	
Outcomes											
Days before death											< .001
Median		168.5		50		67		31		6	
Range		30-548		13-287		35-250		13-133		3-17	
Chemotherapy within 14 days of death	0	0.0	1	6.3	0	0.0	2	9.1	5	71.4	< .001
Hospice	15	83.3	16	100.0	13	72.2	12	54.6	0	0.0	< .001
Days in hospice											.001
Median		8.5		29.5		7		1		0	
Range		0-140		1-268		0-66		0-116			
Death in hospital	3	16.6	0	0.0	2	11.1	12	54.6	2	28.6	.001
Eventual final decision	13	72.2	16	100.0	11	61.1	20	90.9	0	0.0	< .001

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IV, intravenous; SD, standard deviation.

EOL planning. Decisions to stop chemotherapy were usually made by the end of hospitalization, although they were rarely chemotherapy specific. Most of the documented discussions focused on making patients comfortable only. Among those with a final decision to stop chemotherapy, the median number of days between last chemotherapy and final decision was 23.5 (range, 8 to 49 days).

No decision. Patient notes preceding these deaths suggest that they were unexpected, with some oncologists indicating that patients died a “sudden death.” Nonetheless, several notes raise the possibility that oncologists may not have recognized that patients were close to death, as demonstrated by the EHR excerpt in Table 2 from a patient who received chemotherapy and died 6 days later.

Predictors of Discontinuation Processes

Age, sex, race, marital status, baseline ECOG performance status, and lines of chemotherapy did not differ significantly

among the processes (Table 3). However, we did observe an overall difference among the distribution of processes between the standard-care and EPC arms ($P = .03$). When examining each process separately, patients who received EPC were significantly more likely to discontinue chemotherapy after a break ($P < .007$), whereas patients in the standard-care group were more likely to discontinue chemotherapy as a result of hospitalization ($P = .02$). In fact, 17 of the 45 standard-care patients (37.8%) had their chemotherapy discontinued because of hospitalization.

Outcomes of Discontinuation Processes

EOL outcomes among the processes are summarized in Table 3. The processes occurred at significantly different times before death, and subsequent EOL outcomes (eg, hospice referral, length of time in hospice, and terminal hospitalization) were also different. Chemotherapy discontinuation after a break occurred significantly earlier than other processes (break *v* all

other processes). Patients who discontinued chemotherapy with a definitive decision had a higher rate of hospice referral, more days in hospice, and a lower rate of dying in the hospital (definitive decision *v* all other processes). In contrast, those who did not have a discontinuation decision were significantly more likely to receive chemotherapy within 14 days of death.

In multivariable analyses, a chemotherapy break remained associated with earlier discontinuation (break *v* all other processes) after adjustment for age, marital status, and random assignment to EPC ($P < .001$). A definitive decision remained associated with longer duration of hospice (definitive decision *v* all other processes), adjusting for age, marital status, and random assignment to EPC ($P = .002$). In separate analyses, a definitive decision remained associated with greater likelihood of hospice after adjustment for age ($P = .02$), marital status ($P = .007$), and random assignment to EPC ($P = .008$). A definitive decision also remained significantly associated with lower likelihood of death in the hospital after adjustment for marital status ($P = .02$) and random assignment to EPC ($P = .03$) but not for age ($P = .14$).

Discontinuation of Oral Chemotherapy

The median number of days between stopping oral chemotherapy and death was 34 days (range, 0 to 732 days). Patients whose last regimen was oral were more likely to receive chemotherapy within 14 days of death compared with those who received IV chemotherapy ($P = .05$).

Only eight of 48 patients received oral chemotherapy exclusively for their treatment. A majority of patients were switched from IV to oral chemotherapy as their last regimen (40 [83.3%] of 48). The median time between this transition and death was 134.5 days (range, 47 to 965 days). Oncologists documented a variety of reasons for switching from IV to oral chemotherapy (eg, patients later testing positive for *EGFR* mutation or potential benefit of regimen as second-line therapy for those without mutation). However, documentation showed that many patients were switched to oral chemotherapy because the oncologist felt that the patient could not tolerate an IV regimen, viewing oral chemotherapy as lighter. The following EHR excerpt illustrates this: "He asked about his prognosis and we told him he likely had 1 to 4 months to live. We told him that his options were hospice or 'gentle chemotherapy' (targeted agents). He said that he would like to try different chemotherapies." Although it was not uncommon for patients to be offered a choice between oral chemotherapy and hospice after their last IV treatment, six patients were switched to oral chemotherapy either simultaneously with or after hospice referral. Thirty-four patients (70.8%) who received oral chemotherapy as their last regimen were referred to hospice, but one quarter (12 of 48) died in the hospital. The median number of days between hospice referral and death in this group was 12.0 (range, 0 to 375 days).

Discussion

Although current quality metrics focus on the time interval between a patient's last chemotherapy treatment and death, our

study demonstrates that the date of last chemotherapy treatment is not a proxy for when a decision to stop cancer treatment is made. In this sample of patients with metastatic NSCLC, $< 20\%$ had evidence of a definitive decision to stop chemotherapy at the time their chemotherapy was discontinued. For the majority of patients, a substantial amount of time followed the last IV chemotherapy treatment before a final decision to stop chemotherapy was made.

The lag in time between the last chemotherapy treatment and decision to stop treatment may explain previous findings in administrative databases. Studies of EOL care quality indicators have observed that discontinuation of chemotherapy before 14 days of death and hospice referral seem to be related but separate processes.² In our sample, many patients had not received chemotherapy for months, but a decision to stop treatment tended to occur closer to death, as part of hospice discussions. Chemotherapy was most commonly discontinued because of a treatment disruption instead of a decision, whereas hospice referral required a discussion and decision. Understanding that these can be two distinct processes reconciles seemingly contradictory and puzzling observations, such as greater hospice use among patients with advanced cancer between 1997 and 2007, but no earlier discontinuation of other aggressive treatments at EOL.²⁴

Although five different processes were identified, the discontinuation of chemotherapy seemed to occur more often in response to failures rather than futility or lack of benefit. The American Society of Clinical Oncology recommends stopping chemotherapy when evidence-based therapies show no benefit and the clinical value of further treatment lacks supporting evidence,²⁵ but, in weighing the potential benefits and risks of additional chemotherapy, a decision may be guided more by the potential for harm. Documentation of discussions to continue or start new chemotherapies rarely mentioned potential benefit, only a good performance status to tolerate treatment. Patients typically continued to receive chemotherapy until marked physical or functional deterioration requiring a disruption, often for more immediate medical treatment. In fact, $> one$ third of patients in the standard-care arm experienced chemotherapy discontinuation because of hospitalization.

The uncertainty of when a patient might die is a major challenge in stopping chemotherapy well before death. Performance status, which is highly predictive of survival, was the most cited reason for chemotherapy discontinuation. However, the different processes of chemotherapy discontinuation seemed to vary based on how confident the oncologist might be in his or her assessment of the time course of a patient's disease. Oncologists have been shown to overestimate the survival of their terminally ill patients,^{26,27} which could lead to overconfidence in administering chemotherapy to a patient close to death. Taking a break from chemotherapy may demonstrate that oncologists are not fully confident about definitively stopping chemotherapy, even though they recognize a need to discontinue treatment at that time. Gaining the additional confidence needed to make a definitive decision may take oncologists much longer, potentially resulting in delayed hospice referral. Waiting

too long, however, until a necessary treatment disruption or death could signal overconfidence in the decision to continue or missed signs that might have led to earlier discontinuation.

Discontinuing chemotherapy after a treatment holiday or break seemed to result in the greatest amount of time between treatment and death. The greater use of breaks to discontinue chemotherapy may have led to the earlier discontinuation of chemotherapy in patients in the EPC arm of the trial. Breaks are common in oncology practice, and for both patients and oncologists, pausing with a plan for re-evaluation may be a much less threatening discussion than stopping chemotherapy altogether. However, oncologists' documentation did not suggest that they were deliberately using breaks in this way. Breaks seemed to function less like vacations, with clear plans for returning, and more like so-called taking a break in dating or marriage. Even though a clinician may document a plan to reconsider chemotherapy, a break may foreshadow ceasing disease-focused care. A potential hazard of breaks is the delay of earlier hospice referral. Remaining mindful of hospice decisions during a break may reduce this hazard.

Although this study is the first, to our knowledge, to describe the processes of chemotherapy discontinuation, it has limitations. First, because it is based on EHR notes, the documentation may not have fully captured the components of the processes, including who initiated the discussions, the participation of patients in decisions, or possible earlier undocumented treatment discussions. Second, the sample consists of participants in a trial of EPC at one site. Additional processes might be observed at other sites, and the frequencies of the processes will likely vary by institution and geographic region. EPC may have also affected the processes of chemotherapy discontinuation in half the sample, although the processes remained significantly associated with EOL outcomes after adjustment for this factor. Although the distributions of these processes may differ across care settings and populations, our descriptions of the range of processes remain the key contribution of this study.

The processes of discontinuing chemotherapy clearly warrant further research. Prospective observation is needed to understand the thoughts and actions of both oncologists and patients, especially regarding with whom the decision primarily

lies (ie, oncologist, patient and family, or both). Categorization of the processes might also require further elaboration and consist of a series of decisions or steps. Although breaks were observed as the earliest process in this sample, more research is needed before they can become a recommended approach, particularly with regard to the potential impact of being in treatment limbo on patients' quality of life.

As the number of reports in the literature of rates of chemotherapy at EOL grows, chemotherapy discontinuation should not just be considered a date before death; it is a process. Differentiating the processes of discontinuing chemotherapy seems to be meaningful, because these processes occur at significantly different time points before death and may affect subsequent EOL care, such as hospice referral, days in hospice, and death in the hospital. Understanding these processes has the potential to reduce the administration of chemotherapy at EOL by identifying not only practices with better outcomes but also factors that trigger earlier discontinuation.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Processes of Discontinuing Chemotherapy for Metastatic Non–Small-Cell Lung Cancer at the End of Life**

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No relationship to disclose

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No relationship to disclose

Inga T. Lennes

Honoraria: Blue Cross and Blue Shield of Massachusetts

Consulting or Advisory Role: Kyruus

Vicki A. Jackson

No relationship to disclose

Elyse R. Park

No relationship to disclose

Daisuke Fujisawa

No relationship to disclose

Alexi A. Wright

No relationship to disclose

Jennifer S. Temel

Research Funding: Helsinn Therapeutics (Inst)

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