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Timing of Palliative Care Referral and Symptom Burden in Phase I Cancer Patients: A Retrospective Cohort Study

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Abstract

Background—Phase I trials offer advanced cancer patients the opportunity to pursue life-prolonging cancer treatments. In this study, we compared the timing of referral and symptom burden between patients referred to palliative care by Phase I oncologists and those referred by non-Phase I oncologists.

Methods—All 57 patients with advanced solid tumors referred by Phase I to our palliative care outpatient clinic in 2007/2008 were included. The comparison cohort consisted of 114 non-Phase I patients stratified by age, sex and cancer diagnosis in a 1:2 ratio. We retrieved information regarding patient characteristics, Edmonton Symptom Assessment Scale (ESAS), timing of referral and survival.

Results—Both cohorts had the following matched characteristics: average age 57, female 44% and gastrointestinal cancers 47%. At the time of palliative care consultation, Phase I patients were more likely than non-Phase I patients to have a better performance status (ECOG 0-1, 61% vs. 36%, *P*=0.003). ESAS was not different except for better well-being in the Phase I cohort (mean 4.5 vs. 5.5, p=0.03). No difference was found for the duration between M.D. Anderson registration and palliative care consult (13 vs. 11 months, *P*=0.41) and overall survival from time of palliative care consult (5 vs. 4 months, *P*=0.69).

Conclusions—Phase I outpatients referred to palliative care had a better performance status but similar symptom burden as non-Phase I patients. Phase I involvement did not delay palliative care referral compared to non-Phase I. This supports the development of a simultaneous care model.

Keywords

Advanced cancer; Palliative Care; Phase I; Referral timing; Simultaneous care; Symptoms

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INTRODUCTION

Advanced cancer patients usually develop higher symptom burden with disease progression, and have fewer standard treatment options available.[1,2] A small proportion of these patients enroll onto Phase I clinical trials, fueled by the hopes of better disease control and improved survival.[3] While Phase I agents may result in symptom benefit through disease stabilization or shrinkage, they can also be associated with various toxicities and logistical burden, including frequent hospital visits and investigations.[4,5] These, coupled with cancer related symptoms and complications, can significantly compromise patients' quality of life.

Phase I patients generally have a poor prognosis, with median survival of 6-9 months.[6-8] Given the significant morbidity and mortality among Phase I patients, the involvement of palliative care can be potentially beneficial. Palliative care has evolved as a discipline that focuses on improvement of the quality of life of cancer patients and families through early identification, assessment and treatment of symptoms.[9] Timely referral to palliative care is an important indicator of quality of care, as patients gain access to multi-dimensional care early in the trajectory of illness.[10,11] However, studies support that Phase I patients are less likely to consider palliative care, home health aide, counselors and chaplains.[12] Thus, the pursuit of Phase I therapy may potentially delay referral to palliative care.

To date, there is only one study on the symptom burden of Phase I patients compared to non-Phase I patients,[12] and no information on the impact of Phase I involvement on the timing of referral to palliative care. A better understanding of the timing of palliative care referral and symptom profile can provide the foundation for optimizing care for these individuals. Using a retrospective cohort design, we compared the timing of referral and symptom burden between patients referred to palliative care by Phase I oncologists and those referred by non-Phase I oncologists.

PATIENTS AND METHODS

Subjects

The Institutional Review Board at M. D. Anderson Cancer Center approved this study and waived the requirement for informed consent. All patients with advanced solid tumor referred to the outpatient supportive care clinic at M.D. Anderson Cancer Center between January 1, 2007 and Dec 31, 2008 as the first palliative care consultation were identified. Fifty-seven patients were referred by Phase I, and were designated as the Phase I cohort. Among the remaining patients, we randomly selected 114 as the non-Phase I cohort, stratified by age, (<60 or ≥60), sex (male or female) and cancer diagnosis (breast, gastrointestinal, genitourinary, gynecologic, head and neck, lung and other) in a 1:2 ratio.

Patient Characteristics, Symptoms and Timing of Referral

We retrospectively retrieved patient demographics (age, sex, race), cancer diagnosis, timing of diagnosis, encounters with medical oncology, Phase I and palliative care, treatment history, and survival from institutional databases, electronic health records, and Tumor Registry Vital Statistics Database. We also collected information on the Edmonton Symptom Assessment Scale (ESAS), the Memorial Delirium Assessment Scale (MDAS), and Eastern Cooperative Oncology Group (ECOG) performance status at the time of palliative care outpatient consultation.

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Statistical Analysis

We summarized the baseline demographics and symptom profile using descriptive statistics, including medians, means, standard deviations, ranges, and frequencies together with 95% confidence intervals (CI).

We compared the baseline characteristics and symptom profile between the Phase I and non-Phase I cohorts. Comparisons were made using the Student's *t*-test for continuous variables that were normally distributed (i.e. ESAS), the Mann-Whitney test for continuous, non-parametric variables (e.g. prior systemic therapy courses), and the Chi-square test or Fisher's exact test for categorical variables (e.g. MDAS). A two-sided *P*-value of less than 0.05 was considered to be statistically significant.

Timing of palliative care referral was defined a priori based on two intervals, including time from M.D. Anderson registration to palliative care consultation, and overall survival from time of palliative care consult. All time-event analyses were plotted by using the Kaplan-Meier method, and survival curves were compared by the log-rank test.[13,14] Overall survival was calculated from the date of palliative care referral to the date of death from any cause or the date at which the patient was last known alive. Multivariate analysis was performed by using the Cox proportional hazards model with backward elimination.

The Statistical Package for the Social Sciences (SPSS version 16.0, SPSS Inc., Chicago, Illinois) software was used for statistical analysis.

RESULTS

Baseline Characteristics

Table 1 summarizes patient demographics at first palliative care outpatient clinic consultation. Patients referred by Phase I were less likely to present with metastatic disease, and to have more prior chemotherapy regimens compared to those referred by non-Phase I oncologists. Among the Phase I cohort, 6 (11%), 13 (23%), 13 (23%) and 25 (43%) patients completed 1, 2, 3 and ≥4 lines of chemotherapy prior to palliative care consultation, respectively, compared to 33 (29%), 25 (22%), 14 (12%) and 19 (17%) for the non-Phase I group. A small proportion (26%) of patients in the Phase I cohort were seen directly by Phase I without medical oncology involvement from our institution. Among the non-Phase I cohort, 12/114 (11%) had also been seen Phase I, but were referred by non-oncologists to palliative care.

Symptom Profile

The symptom burden at first palliative care outpatient clinic consultation is shown in Table 2. Patients referred by Phase I had better performance status, and were less likely to be delirious (MDAS≥8) at the time of presentation. The two cohorts had similar physical and psychosocial symptoms as assessed by ESAS, although the Phase I cohort had a better overall well being (mean 4.5 vs. 5.5, *P*=0.03) compared to the non-Phase I cohort.

Medical Oncology and Phase I Involvement

Compared to the non-Phase I cohort, patients referred by Phase I had significantly longer survival from diagnosis of advanced cancer (Table 3). Both cohorts were followed by medical oncology for a similar duration (17 vs. 14 months, p=0.36). Patients in the Phase I cohort were referred to Phase I a median of 23 months (95% confidence interval (CI) 11-45 months) from time of diagnosis of advanced cancer, and a median of 6.5 months (95% CI 4.4-8.6 months) before death.

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No difference was found in survival from referring team's last visit (median 28 vs. 41 days, p=0.84); however, the last medical oncology visit happened earlier in the Phase I cohort (200 vs. 41 days, $P<0.001$), suggesting that Phase I oncologists, rather than the referring oncologists, were primarily responsible for the care of these patients in the last few months of life.

Quality of End-of-Life Care

Among all the patients who died, those referred by Phase I were more likely than the non-Phase I cohort to receive chemotherapy within the last 30 days of life (31% vs. 13%, $P=0.014$). The interval between last chemotherapy and death also appeared to be shorter for the Phase I cohort (median 60 days vs. 81 days, $P=0.06$), although this did not reach statistical significance.

Only a small proportion of patients in both cohort were admitted to the intensive care unit within the last 30 days of life (4% vs. 6%, $P>0.99$). We did not detect any differences in the proportion of in-hospital deaths between the two groups (18% vs. 28%, $P=0.21$).

Palliative Care Referral

Patients referred by Phase I had a significantly longer interval from diagnosis of advanced cancer to palliative care consultation, as well as longer interval between first oncology contact and palliative care consultation (Table 3). However, the two key markers of timing of palliative care referral, time from M.D. Anderson registration to palliative care consultation and overall survival from time of palliative care consult, did not differ between the two groups (Table 3). In Cox regression multivariate analysis, only cancer diagnosis was significantly associated with the timing of palliative care referral (Table 4).

The duration between referring team's initial contact and palliative care referral was shorter for patients in the Phase I cohort, suggesting that these patients were referred promptly to palliative care (Table 3). No difference was found in the duration of overlap between palliative care consult and referring team's last visit (median 63 vs. 44 days, $P=0.84$).

Consistent with the above findings, the number of medical oncology clinic visits before palliative care consultation, and the number of palliative care clinic visits until death were similar between the two cohorts (Table 3). Patients in the Phase I cohort had a median of 4 (interquartile range 1.5-10.5) Phase I visits before palliative care consult.

DISCUSSION

In this retrospective cohort study, we found that patients referred to palliative care by Phase I oncologists had a better performance status but similar symptom burden as those referred by non-Phase I oncologists, and were more likely to receive chemotherapy close to the end-of-life. Survival from time of palliative care referral was approximately 4 months for both cohorts, suggesting that Phase I involvement did not delay palliative care referral. This supports the development of a successful simultaneous care model.

One interesting though not completely surprising finding from this study is that the Phase I cohort had a longer overall survival from diagnosis of advanced cancer compared to non-Phase I cohort, suggesting that these patients generally have a less aggressive disease course relative to patients who were not referred.15 In contrast, a number of patients in the non-Phase I cohort deteriorated rapidly, limiting their ability to enroll onto clinical trials.

We found that patients from the Phase I cohort had a better performance status and were less likely to be delirious at presentation to palliative care; this finding is not surprising given

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that patients need to be well enough to be referred for Phase I treatments.15,16 We found that Phase I patients otherwise had similar symptom expression compared to non-Phase I patients. Our findings are consistent with a recent prospective cohort study from a different institution using the Memorial Symptom Assessment Scale.12 Similar to other studies on palliative care populations, fatigue, pain and anorexia were the most common and severe symptoms in both cohorts.17 Importantly, our results support that both Phase I and non-Phase I patients have significant physical and psychological distress at the time of presentation to palliative care outpatient clinic, pointing to the need for intensive interventions.

We had a number of reasons to suspect that Phase I patients could be referred to palliative care later than non-Phase I patients. Phase I treatments were typically offered late in the disease trajectory, when patients have already exhausted all standard treatments. Thus, while the non-Phase I oncologists had ample of opportunities to make palliative care referrals early in the disease course, the timing of referral by Phase I physicians is dependent on when the Phase I consultations take place, which are generally within the last few months of life.

In addition to logistical challenges, the literature suggests that patients on Phase I trials are not psychologically prepared for transition to end-of-life.12,18 Agrawal et al. surveyed 163 patients on Phase I protocol regarding their decision making process. While over 80% of patients stated that they were aware of palliative care and hospice as alternatives to Phase I trial, less than 10% seriously considered these options for themselves.18 Potential explanations include lack of understanding of palliative care services, lack of self-perceived need for support services due to better performance status, and the desire to focus only on cancer treatments. Indeed, patients embarking on Phase I trials generally have heightened expectations in regard to survival and treatment outcomes.19,20 This, coupled with a sense of denial, makes them much less likely to desire palliative care services. Finally, the misconception by some oncologists that a palliative care referral could destroy hope presents another barrier to the referral process.21,22

Despite the many factors that could potentially limit palliative care referral among Phase I patients, we were encouraged to find that Phase I involvement did not delay palliative care referral. The median duration between first Phase I contact and palliative care referral was only 31 days, suggesting that Phase I physicians made their referral relatively quickly without significant delays. Since Phase I physicians work closely with patients with advanced cancer near the end-of-life, they may have a better understanding of the palliative care needs of their patients, and the potential benefits related to a timely referral. For individuals too sick to enroll onto experimental protocol, they may be referred to palliative care for transition to the end-of-life. For other patients participating in Phase I trials, palliative care helps to support them through treatment by optimizing their functional status, symptoms and support systems.

Consistent with this model of integrated care, patients referred by Phase I were more likely to receive chemotherapy within the last 30 days of life. This finding is not unexpected given that these patients were actively seeking further treatments. The administration of chemotherapy close to the end-of-life has been used as an indicator of poor quality of cancer care.23–25 However, this marker is of limited value as an outcome measure since the timing of death cannot be accurately predicted. There are always patients who desire aggressive treatments despite understanding the unfavourable risk:benefit ratio. Finally, the emergence of targeted therapies with lower toxicity profile compared to traditional cytotoxic therapies has allowed sicker patients to receive anti-cancer treatments later in the disease trajectory. Thus, the 30 day criterion may not be appropriate for Phase I cancer patients.

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Close collaborations between Phase I and palliative care under a simultaneous care model can help optimize both quantity and quality of life, while tailoring care to the individuals' needs.[26-28] Clinicians, patients and families should understand that they do not have to choose between Phase I and Palliative care, but could take advantage of both services synergistically. Under this integrated care approach, Phase I oncologists can deliver the latest cancer treatments with the aim of cancer control, while the palliative care team focuses on symptom management, psychosocial interventions, family counseling, and transition of care. Given the significant symptom burden, emotional distress and poor prognosis of Phase I patients, almost all of them may benefit from this simultaneous care approach.

The optimal timing for palliative care referral has not been defined, although the general understanding is that patients were referred late.[29-31] The American Society of Clinical Oncology (ASCO) recently published a position statement supporting the vision of integrating palliative care into oncology practice from the time of cancer diagnosis.[11] In our study of patients who were first referred as outpatients, palliative care involvement was limited to the last 4 months of life, with a median of 4 clinical encounters. Thus, much work remains to be done to bring palliative care earlier in the disease trajectory, ideally before the Phase I visit. Studies from our group and others have demonstrated that palliative care referral is dependent on various factors, including oncologists' perception and attitudes,[21,32] patient characteristics and preferences[33,34] and healthcare infrastructure and policies.[35] Consistent with the literature,[36] we found that cancer diagnosis, which dictates which team of oncologists the patient sees, is a key determinant on the timing of referral to palliative care. While not examined in this study, factors associated with referral to Phase I may include institutional resources, oncologists' attitudes, patient education and preferences, as well as cancer site and stage.[15,37,38]

Our study has a number of limitations. First, data were collected retrospectively. Second, despite the fact that our Phase I and palliative care programs represent a few of the largest programs in the United States, the sample size was small. This is partly because we elected to focus on outpatient referrals as a model of integration. Third, this study only examined the timing of referral, as we did not have access to data of patients seen by Phase I and non-Phase I services, but who were not subsequently referred to palliative care. Fourth, 11% of patients in the non-Phase I cohort had consulted Phase I either before or after palliative care consultation, although they were not referred by Phase I. This "contamination" may have reduced any observed differences in our outcomes. Finally, findings from our study are institution-specific and are not generalizable to other programs. Nevertheless, it showcases how two healthcare teams with seemingly opposing objectives can care for patients collaboratively.

To our knowledge, this is the first study to examine the timing of referral between Phase I and non-Phase I patients. We found that Phase I involvement did not delay palliative care referral in our institution. Despite a better performance status, patients referred by Phase I had significant symptom burden similar to those referred by non-Phase I services, and were more likely to be receiving chemotherapy closer to death. These findings point to the need for interdisciplinary palliative care interventions concurrent with Phase I under a simultaneous care model. While not every patient requires intensive symptom management up front, timely referral can facilitate rapport building, longitudinal psychosocial support, early recognition and treatment of symptoms, and advance care planning. To ensure timely access to comprehensive cancer care for all patients, improvements in reimbursement policy, palliative care resources, education of oncologists, patients and families, and research on novel integration models are urgently needed.

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Condensed abstract

In this retrospective cohort study, we found that Phase I outpatients referred to palliative care had a better performance status but similar symptom burden as non-Phase I patients. Phase I involvement did not delay palliative care referral compared to non-Phase I, supporting the development of a simultaneous care model.

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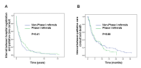

Figure 1. Timing of Palliative Care Referral

Kaplan-Meir curves for (A) Interval between M.D. Anderson registration and palliative care consultation, and (B) Interval between palliative care consultation and death

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Table 1
Baseline Characteristics at Palliative Care Clinic Consultation

	Phase I Referrals (N=57)	Non-Phase I Referrals (N=114)	P-Value
Age (SD)	55 (13)	57 (15)	0.50
Female	25 (44%)	50 (44%)	>0.99
Ethnicity			
Caucasian	40 (70%)	73 (64%)	0.39
African American	9 (16%)	18 (16%)	
Hispanics	4 (7%)	18 (16%)	
Other	4 (7%)	5 (4%)	
Cancer diagnosis			
Breast	5 (9%)	10 (9%)	>0.99
Gastrointestinal	27 (47%)	54 (47%)	
Genitourinary	6 (11%)	12 (11%)	
Gynecologic	3 (5%)	6 (5%)	
Head and neck	3 (5%)	6 (5%)	
Lung	1 (2%)	2 (2%)	
Other	12 (21%)	24 (21%)	
Stage			
Recurrent	0 (0%)	3 (3%)	0.046
Locally advanced	2 (4%)	16 (14%)	
Metastatic	55 (97%)	95 (83%)	
Number of lines of chemotherapy regimens prior to palliative care consultation [1]	3 (2-5)	2 (1-3)	<0.001
Treated with Phase I therapy	43 (75%)	4 (4%)	<0.001
Sequence of team involvement [2]			
Oncology, Phase I, Palliative care	42 (74%)	2 (2%)	<0.001
Phase I, Palliative care	15 (26%)	0 (0%)	
Oncology, Palliative care	0 (0%)	98 (86%)	
Oncology, Palliative care, Phase I	0 (0%)	10 (9%)	
Palliative care, Oncology	0 (0%)	4 (3%)	
Median interval from diagnosis of advanced cancer to palliative care consultation, months (95% confidence interval)	28 (19-37)	12 (9-14)	<0.001
Deaths	49 (86%)	89 (78%)	0.22

Abbreviations: SD, standard deviation

[1] Between the time of advanced cancer diagnosis and palliative care consultation

[2] Denotes the time sequence of patient encounters with oncology, Phase I and palliative care, ordered by the date of first visit to each service

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Table 2
Symptom Burden at Palliative Care Clinic Consultation

	Phase I Referrals (N=57)	Non-Phase I Referrals (N=114)	P-Value
Mean Edmonton Symptom Assessment Scale (SD)			
Pain	5.3 (2.8)	5.1 (3.0)	0.70
Fatigue	5.7 (2.6)	6.4 (2.6)	0.09
Nausea	2.7 (3.2)	2.4 (2.8)	0.48
Depression	2.6 (3.0)	3.5 (2.9)	0.07
Anxiety	2.8 (3.0)	3.5 (2.9)	0.17
Drowsiness	3.7 (3.2)	4.3 (3.2)	0.27
Appetite	5.0 (3.2)	5.7 (3.3)	0.21
Well being	4.5 (2.4)	5.5 (2.8)	0.03
Dyspnea	3.4 (3.2)	3.1 (2.9)	0.52
Sleep	4.8 (2.6)	4.6 (3.2)	0.71
Performance status			
0-1	35 (61%)	41 (36%)	0.003
2-3	19 (34%)	68 (60%)	
4	3 (5%)	5 (4%)	
Delirium (MDAS ≥8)	0 (0%)	10 (10%)	0.032

Abbreviations: SD, standard deviation

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Table 3
Timing of Palliative Care and Phase I Referrals

	Phase I Referrals (N=57)	Non-Phase I Referrals (N=114)	*P*-Value
Median interval in months (95% confidence interval)			
Diagnosis of advanced cancer to death	36 (25-47)	23 (17-29)	0.01
Diagnosis of advanced cancer to palliative care consultation	28 (19-37)	12 (9-14)	<0.001
M.D. Anderson registration to palliative care consultation	13 (8-20)	11 (5-15)	0.41
Palliative care consultation to death	5 (3-6)	4 (3-5)	0.69
First medical oncology contact to palliative care consultation	19 (13-25)	8 (4-12)	0.019
First referring team contact to palliative care consultation	1 (0.6-1.5)	9 (5-13)	<0.001
Median number of clinic visits (interquartile range)			
Medical oncology visits before palliative care consultation	12.5 (4.8-24)	10 (4.5-21.5)	0.45
Palliative care visits until last followup/death	4 (3-7)	4 (2-6)	0.39

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Table 4

Cox Regression Multivariate Analysis for Survival from Palliative Care Consultation[a]

	Hazard ratio (95% confidence interval)	*P*-value
Cancer diagnosis		0.05
Breast	0.52 (0.26-1.06)	0.07
Gastrointestinal	1.0	Reference
Genitourinary	0.87 (0.48-1.59)	0.65
Gynecologic	0.94 (0.43-2.06)	0.88
Head and neck	0.66 (0.31-1.39)	0.27
Lung	0.60 (0.15-2.47)	0.48
Others[b]	0.43 (0.26-0.71)	0.001
Performance status	1.17 (0.98-1.40)	0.09

[a]Variables included in this model were age, sex, race, cancer diagnosis, stage, referring team, performance status at presentation, number of medical oncology visits before palliative care consultation, and number of chemotherapy courses before palliative care consultation. Since this model aimed to identify factors that affect the timing of referral rather than factors that confer a poor prognosis, we specifically excluded symptoms from the analysis as some are known to be prognostic factors (e.g. delirium and dyspnea) that could potentially confound this analysis.

[b]Include all cancer types other than breast, gastrointestinal, genitourinary, gynecologyic, and head and neck cancers. Examples included sarcoma, neurologic, and endocrine tumors.