Post-Discharge Survival Outcomes of Patients with Advanced Cancer from the University of Texas MD Anderson Cancer Center Investigational Cancer Therapeutics (Phase I Trials) Inpatient Unit

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Key Words

Phase I · Cancer · Hospice · Investigational therapeutics · Inpatient · Inpatient admission · Survival · Lactate dehydrogenase

Abstract

Background: Patients with advanced cancer who progress on standard therapy are potential candidates for phase I clinical trials. Due to their aggressive disease and complex comorbid conditions, these patients often need inpatient admission. This study assessed the outcomes of such patients after they were discharged to hospice care. **Patients and Methods:** We performed a retrospective analysis of patients with solid tumor malignancies who were discharged to hospice care from the inpatient service. **Results:** One hundred

thirty-three patients were included in the study cohort. All patients had metastatic disease and an Eastern Cooperative Oncology Group performance status ≥ 3 . The median survival after discharge to hospice from an inpatient setting was 16 days, with a survival rate of 5% at 3 months after discharge. The median survival after the last cancer treatment was 46 days, with survival of 17% at 3 months, and 5% at 6 months. Patients with lactate dehydrogenase (LDH) >618 IU/L had a median post-discharge survival of 11 days versus 20 days for patients with LDH ≤ 618 IU/L. **Conclusions:** Patients with metastatic cancer participating in phase I trials who have poor performance status and require inpatient admission have a very short survival after discharge to hospice. A high LDH level predicts an even shorter survival.

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Introduction

Patients with advanced cancer for whom no effective standard therapy exists that would substantially improve their survival can be referred to phase I clinical trials. Investigational treatments, specifically in the era of targeted therapy and immunotherapy, can sometimes provide an opportunity for controlling disease and extending life. Large studies have shown that phase I trials can offer an overall response rate of 11% and median survival of up to 10 months [1, 2]. Patients with advanced cancer often have complex comorbid conditions in addition to their cancer. These patients may often need an inpatient admission if the cancer progresses, if the investigational treatment causes toxicities, or if patients experience exacerbation of comorbidities or other problems such as an acute infection, small bowel obstruction, failure to thrive, etc. We have shown earlier that patients enrolled in phase I trials who are admitted to an intensive care unit have very poor outcomes [3]. Patients considered to have terminal disease who do not need intensive care unit admission may be directly referred to hospice care or an inpatient palliative care unit. Due to the nature of their disease, these patients often have poor life expectancy. However, to our knowledge, no studies have evaluated outcomes of cancer patients in clinical trials who needed inpatient admission and were subsequently discharged to hospice care. Therefore, we conducted a retrospective study to determine the characteristics of this patient population and outcomes after discharge to hospice. In addition, we evaluated the reasons for admission to the phase I inpatient unit and determined whether these reasons or other clinical characteristics predicted post-discharge survival.

Patients and Methods

This was a retrospective study of patients with metastatic solid tumors who were seen in the phase I clinic at The University of Texas MD Anderson Cancer Center between April 1, 2012, and March 31, 2013. We included consecutive patients who were admitted to our phase I inpatient service and were later discharged to hospice care. Included in this data set was a subset of patients who were transferred from the phase I inpatient service to our Acute Palliative Care Unit for symptom control with the goal of discharge to a hospice setting. The study and treatments were conducted in accordance with the guidelines of MD Anderson institutional review board.

Data Collection

Clinical information was extracted from the electronic medical records including age, sex, tumor type, metastatic sites, Eastern Cooperative Oncology Group (ECOG) performance status at the

Table 1. Patient demographic and clinical characteristics ($n = 133$)

Age, years	
Median (range)	60 (19–83)
Gender	
Male/female	76/57
Race distribution	
White	86 (64%)
Hispanic	24 (18%)
African-American	20 (15%)
Other	3 (2.2%)
Cancer primaries	
Lung	9
Gastrointestinal	42
Breast	17
Genitourinary	5
Gynecologic	22
Endocrine	5
Skin including melanoma	5
Head/neck	13
Sarcoma	6
Others	9
Metastases	
Central nervous system	16
Liver	83
Lungs	90
Reason for admission	
Failure to thrive	20
Dyspnea	13
Pain	26
Infection	15
Hyperbilirubinemia	10
Small bowel obstruction	5
Acute kidney injury	7
Other	37
Lactate dehydrogenase, IU/L	
Median (range)	838 (205–22,133)
Albumin, g/dL	
Median (range)	2.7 (1.3–4.3)
Bilirubin, mg/dL	
Median (range)	0.7 (0.2–16.6)

time of admission, reason for admission, date of last cancer treatment, date of discharge to home or inpatient hospice, date of death, time to death after last cancer treatment, and time to death after discharge, as well as the lactate dehydrogenase (LDH), albumin, and bilirubin levels at the time of admission. The date of death was gathered from the electronic medical record or, in some cases, through follow-up phone calls or the social security database.

Outcome Measurements

The primary endpoint was overall survival (OS) after discharge to hospice after an acute inpatient admission. OS was measured from time of discharge until death or the last follow-up on June 30, 2013. The secondary endpoint was to identify association between OS and clinical characteristics.

Table 2. Univariate Cox proportional hazards regression analysis to determine prognostic factors

Potential prognostic factors	Compared groups	Hazard ratio (95% confidence interval)	<i>p</i> value
Age	≥50 vs. <50 years	0.71 (0.47, 1.07)	0.11
Sex	male vs. female	1.17 (0.83, 1.65)	0.38
Race	white vs. non-white	1.23 (0.96, 1.76)	0.26
Lactate dehydrogenase	>618 vs. ≤618 IU/L	1.48 (1.03, 2.13)	0.032
Albumin	<3.5 vs. ≥3.5 g/dL	1.25 (0.67, 2.32)	0.47
Bilirubin	>1.3 vs. ≤1.3 mg/dL	1.16 (0.80, 1.70)	0.43
Central nervous system metastasis	yes vs. no	1.13 (0.67, 1.91)	0.66
Liver metastasis	yes vs. no	1.00 (0.70, 1.42)	0.98
Lung metastasis	yes vs. no	0.85 (0.59, 1.23)	0.40
Reason for admission	group 1 vs. group 2 ^a	1.35 (0.94, 1.95)	0.10

^a Group 1 included patients admitted for failure to thrive, hyperbilirubinemia, small bowel obstruction, or acute kidney injury. Group 2 included patients admitted for dyspnea, pain, infection, or other causes.

Statistical Analyses

Categorical variables were described using tables, and compared using the χ^2 test. Descriptive statistics were used to analyze continuous variables. The Kaplan-Meier method was used for survival analysis, and the log-rank test was used to compare survival between subgroups. Median survival was described as the median and 95% confidence interval, which was defined as the range of median survival from 2.5 to 97.5%. Univariate Cox proportional hazards regression analysis was used to examine potential prognostic factors for survival (age, sex, race, metastatic sites, laboratory values, and reason for admission) without adjustment for specific factors. Statistical inferences were based on two-sided tests at a significance level of $p < 0.05$. Statistical analyses were carried out using statistical software (SAS version 9.1, SAS Institute, Cary, NC; S-PLUS version 7.0, Insightful Corporation, Seattle, WA, USA).

Results

Study Population

We identified 133 consecutive patients with metastatic solid tumors enrolled on phase I trials who were admitted to and discharged from the phase I inpatient service during the study period. Demographic and clinical characteristics of these patients are listed in Table 1. All of these patients had an ECOG performance status of ≥ 3 at the time of admission, and all were taken off their phase I clinical trials and discharged to hospice.

Survival after Discharge to Hospice

The median survival for these 133 patients was 16 days (interquartile range 5–29 days). The post-discharge OS rates at 1 and 2 weeks and 1, 2, and 3 months were 66, 52,

23, 7, and 5%, respectively. Median survival after last treatment was 46 days (interquartile range 12–48 days). The survival rates after the last treatment at 2 weeks and 1, 2, 3, 4, and 6 months were 93, 74, 37, 17, 10, and 5%, respectively.

We performed univariate analysis to determine prognostic factors for OS (Table 2; Fig. 1). Only raised LDH level (>618 IU/L) was found to be a significant independent predictor of shorter survival after discharge.

We also analyzed the outcomes by reason for the last admission. For the purpose of this analysis, we divided the reasons into 2 groups. The median survival after discharge for patients in the first group (those admitted because of failure to thrive, acute hyperbilirubinemia, small bowel obstruction, or acute renal failure) was 22 days, while the same for the patients in the second group (those admitted for dyspnea, pain, infection, or other causes) was 13 days. There was no survival difference at 4 months (Fig. 2). A total of 19 (14%) and 45 (34%) patients were enrolled in hospice within the last 3 and 7 days of life, respectively.

LDH and Survival after Discharge

The median survival after discharge decreases continuously as LDH increases ($p < 0.0001$, for a Cox proportional hazards model with LDH as a continuous variable on the log scale, hazard ratio = 2.5, 95% confidence interval = 1.6, 3.9). The median OS is 19 days when LDH = 400, 18 days at 800, 15 days at 1,600, 11 days at 3,200, and 6 days at 6,400 IU/L. These estimates are computed from a running Kaplan-Meier smoother run over the data for LDH on the log scale.

Fig. 1. The impact on post-discharge survival of age (a), lactate dehydrogenase (LDH) (b), albumin (c), and central nervous system (CNS) metastasis (d).

Discussion

Candidates for investigational cancer therapeutics most often harbor advanced disease but have exhausted all standard therapeutic options. Those who start on phase I trials often have to stop treatment because of symptoms from progressive disease or treatment-related toxicity. Once patients are no longer able to participate in phase I trials, we transition to a purely palliative approach with symptom management by consulting the palliative and supportive care services and then discharging them through the aid of hospice services. The purpose of this

study was to determine the characteristics and outcomes of these patients with terminal illness who need an inpatient admission and to evaluate the post-discharge survival outcomes.

As one of the largest phase I oncology programs in the world [4], the study population included patients from different racial backgrounds with a wide variety of solid tumors. All patients had metastatic disease and ECOG performance status of ≥ 3 at the time of inpatient admission. We found that these patients fared very poorly after discharge, with a median survival of 16 days (interquartile range 5–29 days), and an OS rate of 5% at 3 months. The

Fig. 2. a Impact of reason for admission on post-discharge survival between the 2 groups. Group 1: failure to thrive, hyperbilirubinemia, small bowel obstruction, and acute renal failure vs. group 2: dyspnea, pain, infection, and other causes. **b** Post-discharge survival: the median survival after discharge decreases continuously as lactate dehydrogenase increases. The median overall survival is 19 days when lactate dehydrogenase = 400, 18 days at 800, 15 days at 1,600, 11 days at 3,200, and 6 days at 6,400 IU/L.

median survival after treatment discontinuation was 46 days (interquartile range 12–48 days), with OS rates of 17% at 3 months, and 5% at 6 months.

Clinical prediction of survival is a very challenging problem oncologists face while caring for patients. Our work provides helpful answers in that regard. Predicting survival for terminal patients is most often based on informal intuitive judgment, which is notoriously inaccurate and overoptimistic [5, 6]. This problem is particu-

larly acute for patients with a life expectancy as short as that of our study population [7, 8]. Our data will help clinicians provide meaningful answers when faced with this question for phase I trial patients who are being discharged to hospice. We also recommend using other objective clinical tools to help predict survival. The Palliative Prognostic Score may be particularly helpful as it has been validated for predicting survival at 30 days [9]. The last cancer treatment date can only be determined retrospectively. However, if a patient has declining functional status or toxicities which would preclude further treatment, then the most recent treatment date can be considered a good substitute, and our findings can be used for those settings as well.

We also found that serum LDH level can help identify a subgroup of patients with even shorter post-discharge survival. Patients with LDH levels >618 IU/L had a median post-discharge survival of 11 days compared to 20 days for patients who had levels below this cutoff. In addition, the median survival after discharge decreases continuously as LDH increases. The median OS is 19 days when LDH is at 400, 18 days at 800, 15 days at 1,600, 11 days at 3,200, and 6 days at 6,400 IU/L.

LDH level has been shown to have a similar predictive capacity for terminally ill cancer patients in the outpatient setting as well [7]. Other studied parameters like serum albumin, bilirubin, and sites of metastasis did not identify any other at-risk subgroups. This is likely due to the very short survival of the study population. The median post-discharge survival of group 1 patients (admitted for failure to thrive, acute hyperbilirubinemia, small bowel obstruction, or acute kidney injury) was 22 days, while the second group of patients (admitted for dyspnea, pain, infection, or other causes) had a shorter survival of 13 days. Although this difference was not statistically significant when survival was compared at 4 months, there was a clear difference in survival when observed at 2 months and earlier.

The American Society of Clinical Oncology and the National Quality Forum have endorsed multiple quality measures for end-of-life care for cancer patients including hospice enrollment within 7 and 3 days of death [10, 11]. A relatively high proportion of our patients, 13 and 34%, were enrolled in hospice within the last 3 and 7 days of life, respectively. These figures support other observations of how we miss opportunities to recognize hospice-eligible patients [12]. Given such poor survival in this population, we recommend that patients undergoing evaluation for investigational therapeutics should also be considered for simultaneous palliative or hospice referral

on an individual basis. The strongest deterrents to early hospice referral are the current Medicare and other insurance reimbursement restrictions. This is despite an extensive body of literature criticizing insurance policies which exclude phase I trial participants from receiving concomitant hospice care [13–15]. Most clinicians agree that joint enrollment in hospice and phase I programs should be allowed whenever a patient is eligible [14]. Also, there exist clinical, ethical, and legal reasons that should prevent such exclusion of phase I trial participants from hospice care [13]. Hence, there is an urgent need for Medicare and private insurance policy reform to allow joint enrollment into phase I trials and hospice. Extending hospice care to these participants has far-reaching consequences. If patients are made more comfortable with hospice care, they will be more likely to complete their investigational regimen and hence contribute more towards our understanding of the investigational agents [13]. Finally, delayed referral to hospice makes it very difficult for patients to have a peaceful, dignified death at home amidst family members; instead, these patients spend their last days in an inpatient hospice facility [16]. Hopefully early referral will deter such an ending.

Lastly, this was a retrospective study, with all the limitations thereof. We could not include patients who were in our phase I programs but were discharged from an outside hospital after an inpatient admission. These results are not applicable for patients who have a good ECOG performance status of ≤ 2 . Our study did not include patients with hematologic malignancies. Given the median age of 60 years for our study population, these results cannot be fully extrapolated to younger patients. None of our study patients needed inpatient admission for elective surgery. Consequently, these results are not applicable for such patients either.

Conclusion

Patients with metastatic cancer participating in phase I trials, who have poor performance status and need inpatient admission, have a very short survival (median survival of 16 days) after discharge to hospice. A high LDH level predicts even shorter survival. This information can help clinicians provide meaningful answers to patients and their families in a similar situation.

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Ethics Statement

Written informed consent for enrollment in clinical trial was obtained from all patients in accordance with the guidelines of the University of Texas MD Anderson Cancer Center Institutional Review Board.

Disclosure Statement

No potential conflicts of interest were disclosed by the authors.

Author Contributions

Conception and design: H.K., G.F., V.S. Development of methodology: H.K., K.H., V.S. Acquisition of data: H.K., A.M., V.S. Analysis of data: All authors. Contributed reagents/materials/analysis tools: All authors. Drafting, review, and revision of manuscript: H.K., A.M., and V.S. wrote the manuscript. All authors critically reviewed and revised the manuscript.

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