Original Article

Targeted Agent Use in Cancer Patients at the End of Life

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Abstract

Context. The use of targeted therapy at the end of life has not been well characterized.

Objectives. To determine the frequency and predictors of targeted therapy use in the last days of life.

Methods. All adult patients residing in the Houston area who died of advanced cancer between September 1, 2009 and February 28, 2010 and had contact with our institution within the last three months of life were included. We collected baseline demographics and data on chemotherapy and targeted agents.

Results. Eight hundred sixteen patients were included: average age 62 years (range 21–97), female 48% and white 61%. The median interval between the last treatment and death was 47 (interquartile range [IQR] 21–97) days for targeted agents and 57 (IQR 26–118) days for chemotherapeutic agents. Within the last 30 days of life, 116 (14%) patients received targeted agents and 147 (18%) received chemotherapy. Regimens given in the last 30 days of life included a median of one (IQR 1–2) chemotherapeutic or targeted agent and 43 (5%) patients receiving targeted agents had concurrent chemotherapy. The most common targeted agents in the last 30 days of life were erlotinib ($n = 25$), bevacizumab ($n = 20$), rituximab ($n = 11$), gemtuzumab ($n = 8$), and temsirolimus ($n = 8$). On multivariate analysis, younger age (odds ratio [OR] 0.98 per year, $P = 0.01$), hematologic malignancy (OR = 6.1, $P < 0.001$), and lung malignancy (OR = 2.6, $P = 0.05$) were associated with increased targeted agent use in the last 30 days of life.

Conclusion. Targeted agents were used as often as chemotherapy at the end of life, particularly among younger patients and those with hematologic

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Key Words
Antineoplastic agents, end of life, palliative care, quality of care, supportive care, targeted agents

Introduction

Our increased understanding of the molecular basis of cancer has resulted in an explosion in the number of targeted therapeutic options.[1,2] Targeted agents include a vast array of monoclonal antibodies, tyrosine kinase inhibitors, and other biologics and are now being routinely used in patient care, with many more under development.[3] Most of these agents are given, with a palliative intent, to patients with advanced cancer.

The use of targeted therapy at the end of life has not been well characterized. Multiple studies have examined the use of chemotherapy among patients with far advanced disease.[4,5] Chemotherapeutic agents are generally associated with significant toxicities and limited benefits when given to patients with poor performance status and/or survival. Thus, published literature considers the use of chemotherapy in the last two to four weeks of life a negative quality-of-care indicator.[6–8]

To our knowledge, only two studies have examined the use of targeted agents at the end of life, one focusing on patients with lung cancer[9] and the other on patients admitted to an acute palliative care unit.[10] A better understanding of the frequency of targeted agent use at the end of life, and the factors associated with their use, would potentially allow us to improve the quality of end-of-life care. In this retrospective study, we determined the frequency and predictors of targeted agent use in the last 30 days of life.

Methods

Study Setting and Eligibility Criteria

The M. D. Anderson Cancer Center Institutional Review Board approved this study and waived the requirement of informed consent. All adult patients in the Houston area who died of advanced cancer between September 1, 2009 and February 28, 2010 and had contact with M. D. Anderson Cancer Center within the last three months of life were included in this study. Patients who transferred care to outside oncologists, relocated to another city, or who were lost to follow-up were excluded. These criteria were chosen so that all patients were either under the direct care of M. D. Anderson Cancer Center or referred to a local hospice, and we were able to reliably capture their information at the end of life.[11]

Data Collection

We collected baseline demographics, including age, sex, race, marital status, cancer diagnosis, and date of advanced cancer diagnosis. Advanced cancer is defined as locally advanced, metastatic, or recurrent disease not amenable to local therapy for solid tumors; advanced stage disease for chronic leukemias and low-grade lymphomas; and recurrent disease for acute leukemias, high-grade lymphomas, and multiple myeloma.

Both chemotherapy and targeted agents, either standard and/or experimental regimens, are available for every tumor type at our institution. The medication name(s) and date of the last documented targeted or chemotherapeutic treatment received before death were retrieved from the electronic chart. Steroids and hormonal therapy were not examined.

Statistical Analysis

We summarized the baseline demographics using descriptive statistics, including means, medians, ranges, interquartile range (IQR), and frequencies. We compared the characteristics between patients who received targeted agents and those who did not receive targeted agents in the last 30 days of life using the *t*-test for continuous, normally distributed variables (e.g.,

age), the Mann-Whitney test for continuous, nonparametric variables (e.g., duration between advanced cancer diagnosis and death), and Pearson's Chi-squared test or Fisher's exact test for categorical variables (e.g., race). We used a multivariate logistic regression model with backward elimination to identify factors associated with targeted and chemotherapeutic agent use in the last 30 days of life. Variables included in the model were age, sex, race, marital status, cancer diagnosis, and survival less than six months between advanced cancer diagnosis and death to account for an aggressive disease course. The same procedure was repeated for chemotherapy use in the last 30 days of life.

To compare the pattern of use between targeted therapy and chemotherapy, we used the McNemar test for binary variables (e.g., treatment within last 30 days of life) and the Wilcoxon test for continuous variables (e.g., median interval between last treatment and death). The Kaplan-Meier method also was used to determine the median duration between last cancer treatment and death by cancer type. The log rank test was used to compare the intervals among various cancer types.

The Statistical Package for the Social Sciences (IBM SPSS version 19.0, SPSS, Inc., Chicago, IL) software was used for statistical analysis. A *P*-value of <0.05 was considered significant.

Results

Patient Characteristics

Table 1 shows the baseline characteristics of the 816 decedents included in this study. Gastrointestinal and lung malignancies were the most common. The median interval between advanced cancer diagnosis and death was only 12 (IQR 5–25) months.

Table 1
Patient Characteristics ($N = 816$)

Patient Characteristics	*n* (%)[a]
Age in years, mean (range)	62 (21–97)
Female sex	390 (48)
Race	
White	499 (61)
Black	178 (22)
Hispanic	97 (12)
Asian	32 (4)
Others	10 (1)
Married	504 (62)
Education	
High school or less	284 (35)
College education	256 (31)
Postgraduate education	63 (8)
Not available	213 (26)
Cancer type	
Breast	71 (9)
Gastrointestinal	178 (22)
Genitourinary	89 (11)
Gynecologic	61 (7)
Head and neck	48 (6)
Hematologic	113 (14)
Other	94 (12)
Respiratory	162 (20)
Months between advanced cancer diagnosis and death, median (interquartile range)	12 (5–25)

[a]Column percentage unless otherwise specified.

Targeted and Chemotherapeutic Agent Use at the End of Life

Three hundred thirty-four (39%) patients with advanced cancer received targeted agents and 533 (65%) patients received chemotherapy during the course of their illness. The median interval between the last treatment and death was 47 (IQR 21–97) days for targeted agents and 57 (IQR 26–118) days for chemotherapeutic agents.

A total of 220 (27%) patients received targeted therapy and/or chemotherapy in the 30-day period before their death. Within the last 30 days of life, patients were more likely to be given chemotherapy than targeted agents (147 [18%] vs. 116 [14%], $P = 0.02$); however, no significant difference was found for the last 14 days of life (64 [8%] vs. 56 [7%], $P = 0.45$). The most commonly used targeted and chemotherapeutic agents are shown in Table 2. The use of targeted agents in the last 30 days of life was associated with chemotherapy use in the same period ($P < 0.001$). Forty-three (5%) patients received both chemotherapy and targeted agents in the last 30 days of life.

In the last 30 days of life, the median number of antineoplastic agents administered was one (IQR 1–1) for targeted agents, one (IQR 1–2) for chemotherapeutic agents, and one (IQR 1–2) for any chemotherapy and targeted therapy among patients who received the respective treatments.

Factors Associated With Targeted and Chemotherapeutic Agent Use in the Last 30 Days of Life

Table 3 shows the separate univariate analysis for patient characteristics associated with

Table 2
Most Commonly Administered Targeted and Chemotherapeutic Agents in the Last 30 Days of Life

Targeted Agents			Chemotherapeutic Agents		
Name	*n*	Approximate Cost Per Month (US$)[a]	Name	*n*	Approximate Cost Per Month (US$)[a]
Erlotinib	25	4823	Gemcitabine	21	5006
Bevacizumab	20	9379	Cytarabine	16	125
Rituximab	11	5746	Cisplatin	13	78
Gemtuzumab	8	19,871	Cyclophosphamide	13	147
Sorafenib	8	7460	Methotrexate	12	8
Temsirolimus	8	5872	5-Fluorouracil	10	65
Bortezomib	7	3998	Capecitabine	10	4858
Cetuximab	5	9907	Paclitaxel	10	161
Lenalidomide	5	8527	Fludarabine	9	1480
Sunitinib	4	6210	Etoposide	8	250
Trastuzumab	4	4276	Carboplatin	7	1650
Alemtuzumab	3	24,506	Doxorubicin liposomal	7	6657
GSK1120212	3	NA[b]	Pemetrexed	7	6995
Others	21	NA	Others	69	NA

NA = not applicable.
[a]We calculated the four week cost of antineoplastic agents for a standard patient (weight 70 kg and body surface area 1.73 m^2) using drug prices from the *Red Book*, 2010.[24] Costs for physician visits, drug administration, and supportive care were not included.
[b]Investigational agent. Pricing is not available.

targeted agent and chemotherapy use at the end of life. We found that young age, hematologic malignancies, and lung cancer were associated with targeted therapy use in the last 30 days of life. Age and cancer type remained significant predictors of targeted therapy use in the multivariate analysis (Table 4).

In the univariate analysis, patients who were young, had hematologic malignancies, and a short interval between advanced cancer diagnosis and death were more likely to receive chemotherapy in the last 30 days of life (Table 3). Multivariate regression analysis showed that hematologic malignancies and a short duration between advanced cancer diagnosis and death were independently associated with chemotherapy administration (Table 4). In contrast, patients with head and neck, lung, genitourinary, gastrointestinal, and other malignancies (e.g., central nervous system, sarcoma, and thyroid) were less likely to receive chemotherapy at the end of life. Table 5 shows the median interval from last anticancer treatment to death by cancer type.

Discussion

In this study, more than one in four patients received palliative systemic therapy within the last 30 days of life, and more than one in eight patients received targeted therapy during this period. Targeted agent use at the end of life was associated with younger age and hematologic and lung malignancies.

At our institution, targeted therapy was used almost as commonly as chemotherapy in the last 30 days of life, with a small proportion of patients receiving both. Our study had similar rates of patients receiving chemotherapy at the end of life relative to other studies using large population databases, although the interval between last chemotherapy and death was shorter in our cohort (median 57 days vs. >120 days).[6,8,12] This difference may be explained by the varying time periods, patient populations, and settings. Furthermore, unlike population studies, we painstakingly reviewed the charts to exclude patients who died without evidence of disease.

The decision to start or stop palliative systemic therapy is an intricate, technical, and often emotionally charged judgment, particularly when the patient is near the end of life.[13] It involves an educated estimation of the risks and benefits by the medical oncologist, guided by clinical evidence and various factors related to the disease, patients, physicians, and practice patterns. As shown in this study, the type of malignancy determines the spectrum of available cancer treatment options, which, in turn, dictates treatment utilization. In addition, the cancer's

Table 3

Patient Characteristics by Targeted and Chemotherapeutic Agent Use in the Last 30 Days of Life ($N = 816$)

	Targeted Therapy in the Last 30 Days of Life			Chemotherapy in the Last 30 Days of Life		
Patient Characteristics	No ($n = 700$) n (%)[a]	Yes ($n = 116$) n (%)[a]	P-value[b]	No ($n = 669$) n (%)[a]	Yes ($n = 147$) n (%)[a]	P-value[b]
Age, years, mean (range)	63 (22–97)	60 (21–90)	0.04	63 (22–97)	60 (21–87)	0.04
Female sex	339 (48)	51 (44)	0.37	316 (47)	74 (50)	0.50
Race						
White	426 (61)	73 (63)	0.41	406 (61)	93 (63)	0.70
Black	158 (23)	20 (17)		148 (22)	30 (20)	
Hispanic	81 (12)	16 (14)		83 (12)	14 (10)	
Asian	28 (4)	4 (3)		24 (4)	8 (5)	
Others	7 (1)	3 (3)		8 (1)	2 (1)	
Married	434 (62)	70 (60)	0.71	418 (63)	86 (59)	0.35
Education			0.06			0.22
High school or less	247 (48)	37 (44)		236 (48)	48 (44)	
College	223 (43)	33 (39)		202 (41)	54 (49)	
Postgraduate	48 (9)	15 (18)		55 (11)	8 (7)	
Cancer type			<0.001			<0.001
Breast	65 (9)	6 (5)		54 (8)	17 (12)	
Gastrointestinal	159 (23)	19 (16)		152 (23)	26 (18)	
Genitourinary	78 (11)	11 (9)		78 (12)	11 (7)	
Gynecologic	60 (9)	1 (1)		49 (7)	12 (8)	
Head and neck	44 (6)	4 (3)		45 (7)	3 (2)	
Hematologic	75 (11)	38 (33)		64 (10)	49 (33)	
Other	84 (12)	10 (9)		84 (13)	10 (7)	
Respiratory	135 (19)	27 (23)		143 (21)	19 (13)	
Months between advanced cancer diagnosis and death, median (IQR)	12 (4–25)	13 (5–26)	0.29	13 (5–26)	8 (3–24)	0.01

IQR = interquartile range.
[a]Column percentage unless otherwise specified.
[b]We conducted two separate univariate analyses using the t-test for continuous, normally distributed variables (e.g., age), the Mann-Whitney test for continuous, nonparametric variables (e.g., duration between advanced cancer diagnosis and death), and Pearson's Chi-squared test/Fisher's exact test for categorical variables (e.g., race).

mutation profile allows oncologists to tailor therapy in the era of personalized medicine. Patients' wishes, prognosis, comorbidities, performance status, adherence, and social support are often taken into consideration in the decision-making process. Oncologists' decisions

Table 4

Factors Associated With Targeted and Chemotherapeutic Agent Use in the Last 30 Days of Life in Multivariate Logistic Regression Analysis[a]

	Targeted Agents			Chemotherapy		
Patient Characteristics	Odds Ratio	95% CI	P-value	Odds Ratio	95% CI	P-value
Age (per year)	0.98	0.97–1.00	0.013	—	—	NS[b]
Cancer			<0.001			<0.001
Breast	1.0	—	Ref.	1.0	—	Ref.
Gastrointestinal	1.5	0.6–3.8	0.45	0.5	0.3–1.0	0.05
Genitourinary	1.8	0.6–5.2	0.28	0.4	0.2–1.0	0.05
Gynecologic	0.2	0.0–1.6	0.12	0.7	0.3–1.7	0.45
Head and neck	1.1	0.3–4.1	0.91	0.2	0.1–0.7	0.01
Hematologic	6.1	2.4–15.4	<0.001	2.2	1.1–4.2	0.025
Other	1.3	0.5–3.9	0.59	0.3	0.1–0.7	0.008
Respiratory	2.6	1.0–6.6	0.05	0.3	0.2–0.7	0.004
Survival less than six months between advanced cancer diagnosis and death	—	—	NS[b]	2.0	1.4–3.0	<0.001

NS = not significant.
[a]Dependent variables included in the models were age, sex, race, marital status, cancer diagnosis, and survival less than six months between advanced cancer diagnosis and death to account for an aggressive disease course.
[b]These variables were included in the multivariate logistic regression analysis but were removed from the models because of the lack of significance.

Table 5
Median Duration Between Last Targeted and Chemotherapeutic Agent Use and Death

Patient Characteristics	Median Days Between Last Treatment and Death (95% CI)		
	Targeted Agents	Chemotherapeutic Agents	Any Targeted or Chemotherapy Agents
Breast	47 (41–53)	48 (39–57)	47 (42–52)
Gastrointestinal	55 (41–69)	53 (44–62)	51 (45–57)
Genitourinary	74 (37–111)	82 (39–125)	74 (48–100)
Gynecologic	61 (31–91)	69 (36–102)	67 (47–87)
Head and neck	63 (29–97)	119 (54–184)	84 (3–165)
Hematologic	26 (15–37)	24 (15–33)	26 (17–35)
Other	59 (36–82)	60 (46–74)	61 (47–75)
Respiratory	40 (22–58)	86 (70–102)	63 (43–83)
Overall	47 (42–52)	57 (51–63)	53 (48–58)
P-value[a]	0.06	<0.001	<0.001

[a]Log rank test comparing the duration among various tumor types.

also are potentially affected by their personal attitudes, experiences, and training. Moreover, local practice patterns, such as drug availability, health care policy, and group culture may have an impact on whether a targeted agent is prescribed.

Targeted agents are often perceived to be more tolerable than chemotherapy. For instance, the National Cancer Institute stated that targeted therapy "may have fewer side effects than other types of cancer treatments."[14] Although nausea and vomiting, myelosuppression, and alopecia generally occur less frequently than with chemotherapy, targeted agents are associated with many unique adverse effects, such as rashes, endocrine abnormalities, and electrolyte imbalances.[15] Folliculitis occurs in up to 80% of patients on epidermal growth factor receptor inhibitors, such as erlotinib and cetuximab, and can be associated with pain, pruritus, and disfigurement.[16,17] Bevacizumab may infrequently cause life-threatening vascular catastrophes and impaired wound healing.[18–20] Everolimus is associated with significant mucositis and electrolyte abnormalities.[21] Sorafenib and sunitinib can both lead to severe fatigue, metabolic changes, and hypothyroidism.[22,23]

In addition to the adverse effects and potential complications requiring hospitalization, there are many less obvious risks to consider when prescribing targeted therapy at the end of life, including frequent hospital visits, invasive investigations, and the tremendous financial burden associated with cancer treatments and supportive care (Table 2).[24] Furthermore, the pursuit of life-prolonging therapy could potentially delay transition of care, diverting patients' precious time and energy to the pursuit of cancer treatments rather than planning ahead.

Palliative therapies are often prescribed with the intention of improving symptom control, sustaining hope, and prolonging survival.[25,26] When a treatment is given in the last 30 days of life, the benefit is arguably negligible. However, it should be noted that clinicians often overestimate survival;[27,28] thus, the use of life expectancy as a criteria for quality of care may be challenging. Instead, performance status has been clearly shown to be an important prognostic and predictive factor.[29] When a patient reaches an Eastern Cooperative Oncology Group performance status of 3 or more (or Karnofsky Performance Status of 40% or less), great caution should be exercised when prescribing palliative systemic therapies.

This is the first study to examine predictors of targeted therapy use at the end of life. We found that hematologic malignancy was associated with targeted therapy use. This is not surprising given that patients with hematologic malignancies generally have a poor quality of end-of-life care.[8] Previous studies have shown that these patients are more likely to receive cytotoxic therapy at the end of life and to be admitted to and die in hospitals and intensive care units and less likely to be referred to palliative and hospice care.[10,30–32] The availability of novel targeted agents for leukemia and lymphoma probably contributed to our observation. For the same reason, erlotinib is often available to lung cancer patients at the end of life. Our findings are consistent with a small

cohort of 36 non-small cell lung cancer patients, in which 21 (58%) received erlotinib or gefitinib in the last three months of life.[9] In contrast, patients with head and neck cancer, central nervous system tumors, and sarcoma were less likely than patients with other tumor types to receive targeted therapy, likely because of the relative lack of standard targeted therapy options for these cancers. We also found that younger patients were more likely to receive targeted therapy at the end of life, consistent with other studies demonstrating that they are generally managed more aggressively than older patients.[10]

This study has several limitations. First, findings in this study are solely based on patients who seek care at our comprehensive cancer center. Our institution offers a wide array of therapeutic options, including numerous clinical trials of novel agents and a large Phase I experimental therapy program. Many patients come specifically to seek further cancer treatments when no standard therapies exist. Because the patient characteristics, practice patterns, and resource availability may differ from other oncology settings, further studies are needed to determine if our findings are generalizable. Second, in addition to the predictors identified above, several factors, such as patient preference, performance status, comorbidities, and clinician characteristics, may determine whether patients receive antineoplastic therapy at the end of life. We were unable to include these variables because they were not routinely documented. Prospective studies could examine these factors in further detail. Third, we did not capture information on treatment toxicities because they were often mixed with patients' underlying symptom burden. Fourth, we only included a short study period. Further studies are needed to examine the trends of targeted agent use at the end of life. Finally, by excluding patients who were not seen by our institution in the last three months of life, we could have inflated the proportion of patients who received chemotherapy or targeted agents at the end of life if these patients were less likely to seek aggressive treatments in the last three months. The opposite also may be true if many of these individuals decided to seek further treatments with their local oncologists after their last visit at our institution. Further studies are required to examine patients' treatment patterns in the community.

In summary, targeted agents were used as often as chemotherapy at the end of life, particularly among younger patients and those with hematologic and lung malignancies. The use of chemotherapy in the last days of life has been established as a quality of end-of-life care indicator.[7,12] Our study raises the question whether targeted therapy also should be considered as another quality-of-care indicator. Given the increasing number of targeted therapeutic options and the growing number of clinical trials, we expect a sustained rise in the use of targeted agents at the end of life. Thus, we urgently need to develop guidelines on when to start and stop palliative systemic therapies for cancer patients with a limited life expectancy.

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