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Prevalence and Determinants of End of Life Chemotherapy Use in Patients with Metastatic Breast Cancer

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Abstract

Background—Cessation of chemotherapy in the last few weeks of life could be an important quality of care benchmark. Proportion of metastatic breast cancer patients who receive end of life chemotherapy is not well described. We aimed to determine the prevalence and determinants of end of life chemotherapy use in patients with metastatic breast cancer.

Methods—A retrospective cohort study using a prospectively collated database of patients with metastatic breast cancer who died between January 1, 2010 and September 30, 2014 was conducted. End of life chemotherapy (EOLC) use was defined as receipt of chemotherapy within 2 weeks of death (EOLC2), and receipt of chemotherapy within 4 weeks of death (EOLC4). Patients who did not receive any chemotherapy in the last 4 weeks before death were categorized as non-EOLC.

Results—We identified 274 patients with metastatic breast cancer, of whom 28 received EOLC2 (10.2%) and 62 received EOLC4 (22.6%). In comparison to non-EOLC, patients receiving EOLC4 were younger and had greater disease burden. Patients in EOLC4 group received more number of lines of chemotherapy. In a multivariable analysis, younger age at metastatic disease and greater number of metastatic organ systems involved were predictors of end of life chemotherapy use.

Conclusions—Prevalence of the use of end of life chemotherapy in our cohort was higher than previously described. More end of life chemotherapy was used in younger women, and those with greater disease burden. Earlier initiation of end of life discussions may be targeted to such patients.

Keywords

Breast cancer; End of life; chemotherapy; prevalence

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Competing interests

The author(s) declare that they have no competing interests

Conflicts of Interest Statement

No conflicts of interest to disclose for all authors.

Introduction

The use of chemotherapy in patients with advanced-stage solid tumors who are nearing death does not prolong life, or improve its quality.[1] The Quality Oncology Practice Initiative of the American Society of Oncology, identified cessation of palliative chemotherapy in the last 2 weeks of life as a benchmark for improving clinical practice.[2] However, identifying the appropriate time to stop chemotherapy is challenging.[3] Several factors may help determine chemotherapy use near the end of life. First, the functional status of a patient is an important determinant;[4] patients with poor functional status rarely benefit from chemotherapy and it may even hasten death.[5] Second, physicians' perceptions of prognosis may influence end of life chemotherapy use. Several studies have shown that oncologists generally tend to overestimate survival in end-stage cancer patients.[6, 7] Third, the patient may prefer to continue with active chemotherapeutic management rather than a symptom-based palliative approach, due to societal pressures or their own perception of disease status.[8–10] Given that these factors are often multi-faceted, patients continue to receive chemotherapy near the end of life, sometimes inappropriately.

A retrospective study from Australia found that 18% of 398 patients with non-hematological malignancies who were treated with palliative chemotherapy continued to receive it within 30 days of death; 8% within 14 days.[11] A Swedish hospital-based study of 374 patients with cancer who died in 2008 after having received palliative chemotherapy during the course of metastatic disease identified that 23% of them received chemotherapy within 30 days of death.[12] The American Surveillance, Epidemiology, and End Results (SEER) data using Medicare claims in patients 65 years and older who received palliative chemotherapy from 1993 to 1996, identified end of life chemotherapy use in 15.7% of patients within 14 days of death.[13] Over the years, there had been trend of increased use of end of life chemotherapy within 14 days of death – 13.8% in 1993, 14.7% in 1994, 15.8% in 1995 and 18.5% in 1996.[13] In contrast, a recent study from a cancer center in the United States reported 3.7% chemotherapy use within 14 days of death; although the study included all patients seen in the institution, and not just those who received palliative chemotherapy.[14]

With regard to patients with metastatic breast cancer, there are very few published studies that report data on the use of end of life chemotherapy. Using Medicare data from 1996, the frequency of end of life chemotherapy use within 30 days of death in breast cancer patients in the states of Massachusetts and California was found to be 8% (n= 612) and 7% (n=73) respectively; the study included all patients who died of cancer, and not just those who received palliative chemotherapy.[15] Data on 335 breast cancer patients in two healthcare districts in Finland between 1995 and 1998 observed that 19.7% of them received chemotherapy within 30 days of death.[16] A Norwegian study using hospital medical records identified 67 breast cancer patients who died in 2005 and 2009 and found that 12% of them received end of life chemotherapy within 30 days and 8% within 14 days.[17] In the Swedish study comprising of patients who received palliative chemotherapy, the prevalence of chemotherapy use within 30 days of death among breast cancer patients was 10.9% (n=46).[12]

A review of the above studies highlights significant variation in frequency of end of life chemotherapy use. Due to the relative paucity of end of life chemotherapy data specific to breast cancer, we aimed to investigate the prevalence of end of life chemotherapy use in patients with metastatic breast cancer at our institution. We also aimed to identify the determinants of end of life chemotherapy use.

Methods

Study population

We retrospectively identified all patients in a prospectively collated database of patients with metastatic breast cancer who were treated at the outpatient clinic of the University of Pittsburgh Cancer Institute between January 1, 2010 and September 30, 2014. We included patients regardless of whether they received palliative chemotherapy. Institutional Review Board approval was obtained from the University of Pittsburgh Institutional Review Board.

Demographic information, tumor characteristics, disease progression and treatment course, and survival data were obtained from the patients' electronic medical records. Pharmacy data was obtained from both the electronic medical records as well as from the medication administration records in patient charts and date of last chemotherapy administration was confirmed through chart review. Brain or leptomeningeal involvement from metastatic breast cancer was defined as central nervous system (CNS) involvement. *De novo* metastatic breast cancer was defined as those patients who had metastatic cancer within two months of diagnosis of primary breast cancer, or those patients who did not have relapsed breast cancer. The number of distant organ sites involved with metastatic breast cancer (such as lung, liver, bone, soft tissue, skin and distant lymph nodes) was identified. Multiple lesions within the same organ were considered as one involved distant metastatic site.

Outcome variables

We defined end of life chemotherapy (EOLC) use based on the date of receipt of last chemotherapy. EOLC2 was defined as receipt of chemotherapy within 2 weeks of death, and EOLC4 was defined as receipt of chemotherapy within 4 weeks of death. Patients who did not receive any chemotherapy in the last 4 weeks before death were categorized as non-EOLC.

Statistical analysis

Means with standard deviations and medians with ranges were used to summarize continuous variables. Categorical variables were summarized as percent of total. We used Chi-square test, Fisher's exact test and Wilcoxon rank sum test, as appropriate, to test for significant associations between patients' baseline characteristics and the receipt of chemotherapy across the three groups; data for the comparisons between EOLC4 and non-EOLC will be described in this article. To address the issue of multiple comparisons, a Bonferroni correction is used, with p-values <0.025 considered statistically significant in the final analysis. Predictors for EOLC4 use versus non-EOLC were determined using logistic regression models. All statistical analysis was performed using SAS 9.4 (SAS Institute, Cary, NC.)

Results

We identified 274 patients who died with metastatic breast cancer (Table 1). 87.6% of the patients were Caucasian, 21.5% had *de novo* metastatic disease, and 37.6% had a history of CNS disease during the course of metastatic breast cancer. 65.7% of patients had hormone receptor positive disease, and 21.2% had HER2 positive disease. 24.1% of our patients had triple negative breast cancer. 12% of patients received no palliative chemotherapy during the course of metastatic disease. Median overall survival was 29 months (range: 2–167).

Of the 274 patients, 28 received EOLC2 (10.2%) and 62 received EOLC4 (22.6%). After excluding patients who did not receive palliative chemotherapy, 11.6% received EOLC2 and 25.7% received EOLC4. There was no statistically significant difference between the groups (EOLC4 versus non-EOLC) with regards to baseline characteristics (Table 1).

Median overall survival from the time of metastatic diagnosis was shorter for patients in the EOLC4 group compared to the non-EOLC group, although this was not statistically significant (Table 2). Patients receiving EOLC4 were younger than those with non-EOLC, with median age at diagnosis of metastatic breast cancer of 50 years (range 35–74) for EOLC4 versus a median of 56 years (range 26–89 years) for non-EOLC group (p-value 0.001). In addition, patients who received EOLC4 had a greater disease burden as noted by the mean number of organ systems involved of 3.5 sites for EOLC4 compared with 2.8 sites for non-EOLC, p=0.0002). The mean number of lines of chemotherapy received for EOLC4 was 4.3 compared with 2.8 for non-EOLC group ($p<0.0001$).

In a multivariable analysis of EOLC4 versus non-EOLC, we found a 49% reduction in EOLC among subjects with CNS disease compared to those without, though this did not reach statistical significance (OR: 0.51; 95% CI: 0.26–1.01; p = 0.05) (Table 4). Similarly, patients with *de novo* metastatic breast cancer were less likely to receive EOLC compared with those who progressed after early-stage breast cancer, though this did not reach statistical significance (OR: 0.45; 95% CI: 0.19 – 1.07; p = 0.07). Younger age at metastatic disease and increasing number of metastatic organ systems involved were predictors of end of life chemotherapy use ($p<0.01$).

Discussion

Our study provides important data on the frequency of chemotherapy use within 2 and 4 weeks of death in patients with metastatic breast cancer, which was 10.2% and 22.6% respectively. Our estimate of the prevalence of end of life chemotherapy use appears to be greater compared to the previous data.[12, 15–17] Such data is extremely challenging to obtain and comparison is difficult given regional and institutional variability in use of end of life chemotherapy, different types of data source, changes in chemotherapy management over the years and the methodological differences between the various published studies. However, there could be several reasons why end of life chemotherapy use is higher in our study. First, our data is more recent compared to the prior studies reporting data on end of life chemotherapy use in metastatic breast cancer (Table 1). Survival of metastatic breast cancer has improved over time and could be associated with greater use of palliative

chemotherapy.[18, 19] Second, we used data from a prospective cohort of metastatic patients and believe that our data on chemotherapy utilization is more accurate. The other studies that report the frequency of chemotherapy use in metastatic breast cancer used a retrospective study design and are prone to bias, potentially resulting in underestimation of prevalence rate.[12, 15–17] Our sample size is also much larger when compared to the Norwegian and Swedish studies which were also similarly based on hospital records.[12, 17] Therefore, it is likely that our data on the prevalence of end of life chemotherapy use in metastatic breast cancer patients may be closer to the actual rates. Third, as compared to the Scandinavian countries, palliative chemotherapy administration may be more prevalent in the United States. For instance, the studies from Finland and Norway reports a prevalence of palliative chemotherapy of 37% and 52% respectively compared to 88% in our study.[16, 17] Fourth, patterns of practice as determined by the oncologists in an institution or group may also dictate the use of end of life chemotherapy, and could cause variation in frequency of end of life chemotherapy use.

In addition to providing data on prevalence, we also investigated the determinants of end of life chemotherapy use in breast cancer. Patients who were younger, and had greater burden of disease were more likely to receive end of life chemotherapy. The EOLC4 group had a shorter survival after diagnosis of metastatic disease compared to non-EOLC4 suggesting a more aggressive disease course in those who received end of life chemotherapy. Patients with CNS disease and those who had *de novo* metastatic disease were more likely not to receive end of life chemotherapy, though these associations did not reach statistical significance.

Studies have consistently shown that patients who receive end of life chemotherapy are younger.[11, 20, 21] Older patients are more likely to value quality of life over life prolonging measures as compared to younger patients.[22] The fact that patients with greater disease burden received more end of life chemotherapy could reflect the aggressiveness of the disease or may also be due to the fact that physicians are not very good at predicting survival.[7] The emphasis on using functional status as a surrogate for longevity may contribute to this factor. Although good functional status is used as a surrogate for chemotherapy benefit, there are limitations to such an assumption. A prospective cohort study of 158 patients with advanced stage cancer identified a detrimental effect of chemotherapy on quality of life near death in those with good performance status at baseline.[5]

Discussions between physicians and patients regarding end of life care were found to take place a median of 33 days prior to death.[23] Those patients who had end of life discussions earlier were less likely to receive aggressive measures before death.[23] Therefore, earlier initiation of end of life discussions may be targeted to patients who are at risk for a more aggressive disease course, such as younger patients, and those individuals with greater disease burden as noted by the number of organ systems involved with cancer.

However, there are several potential barriers to discussing end of life care. An oncologist might be biased due to an anecdotal experience of a patient responding to chemotherapy who only had a limited life expectancy. There might be hesitation in recommending stopping

chemotherapy as it might be equated by the patient as ‘giving up’ or ‘losing hope’ or ‘doing nothing’. With regards to the financial incentive of chemotherapy use, Medicare reimbursement was not found to be associated with more end of life chemotherapy use in a study on patients who died with cancer between 1995 and 1998, although a more recent study noted a reduction in chemotherapy use at the end of life after implementation of payment reform.[24, 25] However, a positive incentive for advance care planning discussions with the patient may result in a decrease in prevalence of end of life chemotherapy use. In the United States, the Centers for Medicare and Medicaid Services will reimburse health care providers for end of life discussions.[26]

Our study has a few limitations. We did not prospectively collect information on quality of life or functional status as it could not be accurately captured from the medical records. Additionally, the smaller sample size in our study could preclude a more detailed subset analysis. Another limitation might be related to the external validity of our study, as ours was a single institution study. Oncology practices and resource utilization might substantially differ by both institution and country.

Conclusions

Appropriately timed cessation of chemotherapy is critical in providing optimal care in patients with end stage cancer. There is a growing concern that chemotherapy administration during the last month of life might not be effective, both in terms of prolonging survival and alleviation of symptoms.

In summary, our study describes the epidemiology of end of life chemotherapy use in metastatic breast cancer at a major teaching hospital in the United States. An informed patient along with timely discussion about goals of care, preferably early on in the disease course, can lead to decreased utilization of chemotherapy towards the end of life, and better quality of life.

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List of abbreviations

EOLC	End of Life Chemotherapy
EOLC2	End of Life Chemotherapy use within 2 weeks of death
EOLC4	End of Life Chemotherapy use within 4 weeks of death
CNS	Central Nervous System

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Table 1

Baseline characteristics

	EOLC4 N=62		Non-EOLC N=212		EOLC4 vs Non-EOLC
	N	**(%)**	**N**	**(%)**	***p-value***
Race (n=271)					
Caucasian	52	(84%)	188	(89%)	
Other	8	(13%)	23	(11%)	0.60
Histology (n=268)					
Ductal	55	(89%)	165	(78%)	
Others	5	(8%)	43	(20%)	0.028
***De novo* metastatic**					
No	55	(89%)	160	(75%)	
Yes	7	(11%)	52	(25%)	0.026
HR Status (n=272)					
Negative	21	(34%)	71	(33%)	
Positive	41	(66%)	139	(66%)	0.99
HER2 Status (n=254)					
Negative	50	(81%)	146	(69%)	
Positive	12	(19%)	46	(22%)	0.45
Subtype (n=254)					
HER2+ HR−	2	(3%)	19	(9%)	0.10
HR+ HER2+	10	(16%)	27	(13%)	0.69
HR+ HER2−	31	(50%)	99	(47%)	0.83
TNBC	19	(31%)	47	(22%)	0.36
CNS Disease					
No	39	(63%)	132	(62%)	
Yes	23	(37%)	80	(38%)	0.93

Table 2

Survival, progression of disease, and lines of chemotherapy

	EOLC4 N=62	Non-EOLC N=212	EOLC4 vs Non-EOLC (p-value)
Median Survival months (range)	21 (2 – 104)	32 (2 – 167)	0.04
Age at diagnosis of primary cancer median (range)	47 (31–71)	52 (25–88)	0.003
Age at metastatic cancer diagnosis median (range)	50 (35–74)	56 (26–89)	0.001
Number of metastatic sites mean (SD)	3.5 (1.2)	2.8 (1.3)	0.0002
Total lines of chemotherapy mean (SD)	4.3 (2.4)	2.8 (2.3)	<0.0001

Table 3

Likelihood of receiving EOLC based on a multivariate logistic regression model

Effect	Odds Ratio (95% Confidence Interval)
CNS disease (Yes vs No)	0.51 (0.26–1.01)
Age at metastatic breast cancer diagnosis	0.97 (0.94–0.99)
Number of metastatic organ systems involved	1.47 (1.16–1.87)
***De novo* metastatic disease (Yes vs No)**	0.45 (0.19–1.07)