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Is Breast Cancer Treatment in the End of Life Less Aggressive?

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Abstract

There is overuse of palliative systemic therapy in the end of life of breast cancer patients, but the growing awareness of this practice and the emphasis put in quality of end of life care might be shifting this practice. We hypothesized we could observe: more implementation of palliative strategies; less administration of palliative systemic anti-cancer therapy and decreased aggressiveness of cancer care in the end of life.

We characterized the shifting trends in use of palliative chemotherapy administration and palliative care approaches in different institutions and times. We selected women that died of breast cancer during six years, from 2007 to 2012, and were treated in a central acute care general hospital and compared it with the breast cancer patients that died in 2003 and were treated in a large cancer center. We analyzed a total of 232 patients: the more recent group has 114 women and the initial cohort has 118. We used descriptive statistics to characterize chemotherapy in the end of life and use of palliative care resources.

We showed increased: referral to palliative care inpatient and outpatient teams,referral to outpatient pain clinics,use of palliative radiotherapy and deaths at hospices instead of at acute care hospitals. Chemotherapy is still prolonged until the end of life, notwithstanding we showed a decrease in such practice. Other indicators of agressiveness, namely hospital admissions, have also shown a decrease.

We showed there is more integration of multidisciplinary palliative care and less aggressiveness in the treatment of breast cancer patients, namely, decreased use of palliative anti-cancer treatment and decreased acute care hospital admissions. Nonetheless, systemic chemotherapy is still used until too late and the integration of oncology and palliative medicine in the care of breast cancer patients in the end of life is lacking.

Keywords: End of life; Aggressiveness; Palliative chemotherapy; Palliative care; Metastatic breast cancer; Temporal trends

Introduction

Cancer remains a leading cause of death in developed countries. Namely, breast cancer is a public health problem since it is the most frequent cancer in incidence, prevalence and mortality in women [1]. Metastatic breast cancer patients have longer median survival than other metastatic solid tumor patients, making this population a challenge for the practicing oncologist [2]. Overuse of anti-cancer therapy is an important quality-of-care issue, as are other indicators of aggressiveness in cancer care in the end of life, like the use of acute care hospital facilities, emergency room admission, palliative radiotherapy and surgery. An aggressive approach to cancer treatment in the end of life can have negative effects on quality of life, cost and survival. The early integration of palliative care has shown to be beneficial in health related quality of life endpoints as assessed by patient reported outcomes, reduced chemotherapy administration, cost reduction and survival [3].

Cancer end of life research shows across cancer types and countries that 20% of patients are being treated with systemic palliative chemotherapy in the last month of life [1-5].

Simultaneously, nowadays more emphasis has been put on directing patients towards a more symptom directed, patient centered care model that involves a diverse team of health care providers, adopts shared decision making, enables patient empowerment and has a biopsychosocial approach to the end of life. However, health systems still lack integrated palliative care teams, hospice care beds, telephone availability 24 h per day and home care for cancer patients in the end of life. Most cancer patients die without ever being taken care by health care teams specialized in palliative care in acute care beds, although increasing awareness is prompting creation of such competences in medical training, chronic or palliative care beds and availability of home care. There are very few home care visits by health care teams who provide specialized care to cancer patients in the end of life, and, specifically, the interaction between large acute care institutions or cancer centers and primary care teams, that provide home care visits, is lacking. This generates anxiety that patients must continue to have their care provided by large hospitals or cancer centers instead of transferring care to proximity palliative health care units in a continuum of care with the team that provided anti-tumor directed therapy.

We had previously presented data regarding aggressiveness of cancer care in the end of life using data from a comprehensive cancer center 4. At the time, a third of our sample size was composed of metastatic breast cancer patients. We analyzed another population of similar size from a central acute care hospital, 6 years later. With this data we aim to [1] characterize end of life care to metastatic breast cancer patients in different institutions and in different time points; [2] show trends in implementation of palliative care strategies; and in aggressiveness of cancer care through systemic anti-cancer treatments, emergency room, hospital and intensive care unit admissions.

Methods

Patients

We analyzed two cohorts of patients. The oldest cohort, from a comprehensive cancer center, were all patients with BC that were treated in the medical oncology department with palliative systemic chemotherapy that is systemic chemotherapy for non-curable locally advanced or metastatic breast cancer, and had died in 2003. In an attempt to quantify the proportion of patients with locally advanced or metastatic breast cancer that were treated with systemic chemotherapy in the medical oncology department, we also collected data on all breast cancer patients treated in the cancer centre who died in 2003. This review was conducted with the approval of the institutional ethics committee.

The more recent cohort, from a general acute care hospital, were all patients with breast cancer that were followed in the medical oncology unit and that died between 2006 and 2012. In this cohort, similarly, we did not select only those patients that were treated with palliative systemic chemotherapy, that is systemic chemotherapy for non-curable locally advanced or metastatic breast cancer, but all the patients that died of breast cancer in the institution during that period. This retrospective chart review was conducted with the approval of the institutional ethics committee. The institutions are different but half of the oncologists of the acute care hospital were trained in the cancer center, so the cancer care provided is similar. These are both public hospitals and they both have available an inpatient and an outpatient palliative care team, as well as a pain clinic. Both these care structures have dedicated physicians and nurses and have a telephone number that is daily available for patients at home. Home visits by these teams are not implemented routinely. Because estrogen receptor positive breast cancer is amenable to endocrine manipulations during long periods of metastatic disease we chose to define therapy as any systemic anti-cancer therapy for metastatic breast cancer that includes chemotherapy and endocrine therapy.

Collected data

Demographic data included sex and age. Cancer-related data included date of diagnosis and death and date of documentation of locally advanced or metastatic breast cancer, which from now on we will designate as metastatic breast cancer. Regarding administration of systemic therapy, data were collected on its use in the treatment of metastatic breast cancer. For those patients that were treated with chemotherapy for metastatic breast cancer further data were collected on potential indicators of aggressiveness of treatment. These included the number, and duration of each chemotherapy regimens, chemotherapy toxicity and chemotherapy response. In the initial cohort we only collected data on the systemic therapy regimens used in the last three months of life, in the recent cohort we collected data throughout the course of metastatic breast cancer. The duration of a chemotherapy regimen was defined as the time between the first and the last day of administration of the drug(s) that were part of each regimen. In this group of metastatic breast cancer, we also recorded palliative care interventions, namely, outpatient consultations with the palliative health care team and in the pain clinic. We also recorded interventions by mental health practitioners like psychiatrists and psychologists. Palliative radiotherapy, generally to bone or brain metastasis or any other metastatic lesion was similarly recorded. Data were collected through the institutional database and from patient clinical charts. Population-based death certificates were used to complement clinical chart data, assuring that no deaths were missed. Median and ranges were used as descriptive statistics. Chi-square statistic was used to compare categorical data. All data were collected and treated in IBM SPSS Version 20.0.

Results and Discussion

Patient related data

The whole cohort has 232 patients. The initial cohort has 118 and the recent one has 114. The median age of the population at diagnosis was 60 years, for both cohorts.

The age range is between 18 and 95 years of age (Table 1). The oldest cohort had no men and the recent cohort had 2 men. Therefore there were 0.8% of male patients in the analyzed group, which in accordance to the frequency of breast cancer in men.

Cancer related data

Breast cancer characteristics are similar between the two populations (Table 1). About initial breast cancer, we recorded data on histologial subtypes, staging, estrogen receptor status and treatment modalities. Concerning metastatic breast cancer, we recorded data on median survival and locoregional or distant organ relapse.

Comparative characteristics of BC		Initial cohort (n=118)	Recent cohort (n=114)	p value
Age incidence	median (range)	60 (32-92)	60 (18-95)	1
Histology	Invasive carcinomas of no special type (NST)	110 (93%)	107 (94%)	0.8
	Lobular carcinoma	3 (2.5%)	3 (2.6%)	1
	Mucinous carcinoma	2 (1.7%)	2 (1.7%)	1
	Metaplastic carcinoma	2 (1.7%)	1 (0.9%)	0.5

	Medullary carcinoma	1 (0.9%)	1 (0.9%)	1
Disease stage at presentation	I (T1N0)	1 (0.9%)	2 (1.7%)	0.5
	II (T1-2 N1)	64 (54%)	68 (60%)	0.0002
	III	22 (19%)	25 (22%)	0.6
	IV	31 (26%)	19 (17%)	0.08
ER status	positive	63 (53%)	56 (49%)	0.5
	negative	37 (47%)	44 (51%)	0.5
Treatment at presentation	Surgery	93 (79%)	83 (73%)	0.5
	Chemotherapy	94 (80%)	83 (73%)	0.0002
	Radiotherapy	94 (80%)	90 (79%)	0.6
	Endocrine therapy	65 (55%)	56 (49%)	0.08
MBC	median survival (months)	24	20	
Location of organ metastasis	Bone	36 (32%)	46 (40%)	0.2
	Locoregional	37 (30%)	35 (31%)	0.8
	Lung	24 (20%)	15 (13%)	0.1
	Liver	10 (9%)	11 (10%)	0.8
	Brain	4 (3.5%)	4 (4%)	1
	Ovaries & peritoneum	3 (1.7%)	3 (2.6%)	1

Table 1: Comparison of the two populations: demographics, early BC and MBC variables. Chi-square test was used to show populations are comparable. P values lower than 0.05 are considered significant.

Palliative care team health care related data

Referral to pain clinic increased significantly in the more recently treated patients as well as shared care by a multidisciplinary palliative team and use of palliative radiotherapy. Only psychiatric referral remained constant through time and both institutions. Regarding place of death, the great majority of metastatic breast cancer patients are still dying in the hospitals that first treated their breast cancer, in our case, the comprehensive cancer center and the general acute care hospital where they were initially treated. However in this time frame, there are significantly more patients dying in hospices and chronic care facilities, and there has been a shift towards dying more at home. In this study, we measured other indicators of aggressiveness, for the patients treated with chemotherapy in the last three months of life, we were able to show a significant decrease in the admissions to the medical oncology ward and a decrease in the days of admission. We saw a trend towards more emergency room visits and less intensive care unit admissions, but it was not significant (Table 2).

Palliation, location of death, systemic anti-cancer treatment and other aggressive care for MBC		Initial cohort (n=118)	Recent cohort (n=114)	p value of chi-square test for difference
Palliative interventions	Pain clinic	12 (10%)	58 (51%)	$3.8x10^{-8}$
	Palliative care consultation	5 (4.2%)	26 (23%)	$1.6x10^{-4}$
	Psychiatry	10 (8.4%)	18 (16%)	0.1
	Palliative radiotherapy	8 (6.8%)	63 (55%)	$6.7x10^{-11}$
Location of death	Hospital where was treated	108 (91.5%)	80 (70%)	0.04
	Another hospital	0 (0%)	5 (4.4%)	0.02
	Hospice	0 (0%)	16 (14%)	$6.3x10^{-5}$

	Home	2 (1.7%)	3 (2.6%)	0.6
	Unknown	8 (6.8%)	10 (8.8%)	0.6
Patients treated systemic	15 days	32 (27%)	13 (11%)	0.004
anti-cancer therapy	last month	45 (38%)	31 (27%)	0.1
	last 2 months	67(57%)	49 (43%)	0.09
	last 3 months	80 (68%)	58 (51%)	0.06
Other indicators of aggressiveness in the patients treated in the last three months	Patients admitted	74/80 (93%)	53/58 (91%)	0.06
	Hospital admissions	284	174	2.7x10^{-7}
	Days in hospital	1725	1002	2.2x10^{-16}
	Patients ER visits	66/80 (83%)	51/58 (88%)	0.16
	Emergency room admissions	166	201	0.06
	Intensive care unit admissions	2 (2.5%)	0	0.15
Patients starting treatments in the last three months	A new regimen	38 (32%)	28 (24%)	0.2
	A 2nd regimen	6 (5%)	2 (1.7%)	0.1
	First ever regimen for MBC	19 (16%)	5 (4.4%)	0.004

Table 2: Comparison of the two populations: MBC care variables. Chi-square test was used to show differences. P values lower than 0.05 are considered significant.

Chemotherapy in the end of life

In the initial sample, we have nearly 30% of patients teated with systemic chemotherapy in the last two weeks of life. There are nearly 40% of metastatic breast cancer patients treated with systemic chemotherapy in the last month of life. Regarding the last two months of life, nearly 60% of the patients were being treated with systemic chemotherapy and in the last three months of life this percentage rises to close to 70% (Table 2). We could show with this study that this trend is changing. In the recent cohort, only 11% of patients were being treated with systemic treatments in the last two weeks of life. Nearly 30% of the metastatic breast cancer patients were being treated with systemic therapy in the last month of life. Forty three percent of metastatic breast cancer patients received systemic anti-cancer treatments in the last two months of and nearly 50% in the last 3 three months. There is a statistically significant change towards less systemic anti-cancer therapy administration in the last 15 days of life of metastatic breast cancer patients. There is less administration in the several intervals studied; last month, two months and three months; but the difference is not statistically significant.

We analyzed systemic therapy regimens in the last three months of life in greater detail. The median amount of different regimens in both groups is 1. In the initial cohort there is one patient undergoing a third regimen of chemotherapy but it was only one administration on the day of death. In the more recent cohort there is no patient with a third regimen.

Regarding the question if patients are being started on new regimens in the last three months of life, we saw thirty-eight such patients in the initial cohort and 28 in the recent cohort. If metastatic breast cancer patients are being treated for the first time with palliative systemic chemotherapy in the last 3 months of life, we have continued to observe this practice. Although it is decreasing with the comparison of the two populations. The initial cohort has 16% of patients in this condition and the recent one only 4%. In those 19 patients (16%) there were three women that even started a second regimen after the failure of the first.

Recent cohort (n=114)	Systemic therapy data
No systemic therapy	28 (25%)
1 regimen	18 (16%)
2 regimens	16 (14%)
3 regimens	14 (12%)
4 regimens	10 (8.8%)
5 regimens	5 (4.4%)
6 regimens	23 (20%)
Median regimens	2

Table 3: Number of regimens of systemic anti-cancer therapy used during the care for MBC patients in the recent cohort

As has been said, in the more recent cohort we collected data on the whole spectrum of systemic anti-cancer treatments for metastatic breast cancer, without focusing only on the last three months, like we did in the earlier cohort. As such, we have data on the number of regimens administered during metastatic breast cancer natural history, which is six in 20% of the patients. Patients treated with less regimens are less frequent. In Table 3 Regarding, subsequent regimens we could show that the median duration of each regimen decreases in a statistically significant way, as decreases the number of treated patients. We were able to show a trend towards less clinical response and more resistance to subsequent regimens, although not statistically significant (Table 4).

Systemic therapy regimens, recent cohort (n=114)	Median duration of regimens & range (days)	Number treated patients (% of population)	Number of patients w/response or stable disease (%)	Number of patients w/ progression (%)
1st	87 (1-736)	86 (75%)	22 (26%)	64 (74%)
2nd	92 (1-562)	68 (60%)	20 (29%)	48 (70%)
3rd	96 (7-1360)	52 (46%)	13 (25%)	39 (75%)
4th	54 (1-511)	38 (33%)	10 (26%)	28 (74%)
5th	67 (1-790)	27 (24%)	4 (15%)	23 (85%)
6th	59 (1-331)	23 (20%)	3 (13%)	20 (87%)
p-value chi square test	0.001	5.5×10^{-12}	0.08	0.7

Table 4: Characteristics of each subsequent systemic anti-cancer treatment regimen used to treat the MBC patients of the recent cohort. Median duration, numbers of patients and response or progression are recorded. Response is defined by objective response or symptomatic response. Objective response is assessed by observation or imaging.

Discussion

The stage distribution and estrogen receptor status is different in this population than in a population of unselected breast cancer patients because these women died of metastatic breast cancer, therefore they have a higher TNM stage at presentation and less estrogen receptor positive tumors. The median survival of metastatic breast cancer patient population is as reported in the literature [2].

Palliative care referral has increased from 4% to 23% in the current cohort. We found only 2.6% of women dying at home, in Canada this percentage was 6.9% 10 years ago[6].

Despite the constant increase of therapeutic armamentarium available to treat metastatic breast cancer patients we were able to show a trend towards less overuse of systemic therapy in the end of life of metastatic breast cancer patients. Unlike other frequent metastatic solid tumors with high mortality like lung, colon, gastric, head and neck and pancreatic carcinomas, where mainly palliative systemic chemotherapy is the mainstay of treatment, in metastatic breast cancer endocrine therapy represents a sizable proportion of systemic treatments. For this reason, we were expecting less administration of palliative systemic chemotherapy in the end of life. But, on the other hand, in metastatic breast cancer there are numerous regimens available to treat patients. This may be one of the reasons why 20% of these patients were treated with six different drug regimens, these are more regimens than those used to treat other disseminated carcinomas [7]. The median duration of different systemic chemotherapies is also higher than in other solid tumours [7]. We could show that metastatic breast cancer patients are treated with more systemic chemotherapy regimens and that they respond for longer. Metastatic breast cancer patients have lesions that respond until very late in their disease course, we were able to show a fifth of patients exibiting response to any particular chemotherapy regimen. This data shows that metastatic breast cancer patients are a particularly sensitive group of patients regarding chemotherapy administration in the end of life.

Contrary to our work, a North American study looking at trends in aggressiveness of care in patients with neoplasias in United States and Canada, shows more aggressiveness over time[8]. The years and intervals are not the same, but, in this study, the diagnosis of metastatic breast cancer is an independant predictor of aggressiveness.

Our work has an important weakness, we do not compare completely equivalent populations. The two institutions are independent health care providers and the majority of the physicians caring for the patients are unrelated although half of the physicians in the acute care hospital were originally trained in the cancer center. Both institutions have the same philosophy of care and both have the availability of palliative acre teams, that have evolved to more integration, specialization and differentiation in the years analyzed. Both institutions are in the same geographical area of the country and have the same funding from the Ministry of Health. The social, cultural, economic and insurance coverage background of the patients cared for is very similar. The comprehensive cancer center, as expected, treats more metastatic breast cancer patients. To overcome this, and to study a similar sample size, we joined the patients who died of metastatic breast cancer during six years in the general hospital to to the initial cohort of metastatic breast cancer patients.

We were able to confirm our hypothesis that there is more integration of multidisciplinary palliative care and less aggressiveness in the treatment of metastatic breast cancer patients, namely, use of palliative anti-cancer treatment and hospital admissions. Nonetheless, systemic therapy is used until too late with under utilisation of palliative medicine.

It vital to start conducting prospective research in end of life questions. If we continue to work retrospectively we will always be forced to collect data from clinical records that are not standardized and therefore we might be comparing different realities and collecting incomplete data. Novel anti-cancer drugs are approved, that is what patients, society, scientists, pharmaceutical companies and oncologists strive for, but what about the end of life of cancer patients, 50% of cancer patients die of cancer. We are afraid the current health care model is not providing the best possible care to cancer patients in the end of life. We lack reliable, reproducible and standardizable instruments to assess and measure care delivered in the end of life of cancer patients. Furthermore, we must measure end of life care routinely. We are not changing the focus of our expectations and those of our patients and families from the next new drug to reduce the dimensions of metastasis and eventually to prolong life to address end of life objectives and wishes. Are oncologists the best trained group for this task or should they acquire palliative care and communication competences or work in an integrated model with palliative care teams [9].At the level of health care recipients, there should be more information for empowering decisions; patients are convinced palliative chemotherapy is much more efficacious than it is [10]. It is time for cancer care providers to discuss terminal patients in a specific end of life multidisciplinary team similar to the one implemented for early cancer cases. The palliative care, pain, mental health, nutrition and radiotherapy health care teams will undoubtedly enrich the care provided to patients with metastatic solid tumors reaching the end of life.

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