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Population-based trends in systemic therapy use and cost for cancer patients in the last year of life

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ABSTRACT

Background The use of systemic therapy near the end of life can expose cancer patients to severe toxicity for minimal survival gain and comes with a high cost. Early palliative care is recommended, but there is evidence that aggressive care remains common. To better understand those patterns, the present study set out to describe trends in systemic therapy use and cost for cancer patients in the last year of life.

Methods Using the BC Cancer Registry, a retrospective population-based cohort of cancer decedents (2002–2007) was identified and linked to systemic therapy records. The outcomes of interest were any systemic therapy use and total systemic therapy costs during the last year of life. Multiple logistic regression (systemic therapy use) and generalized linear regression (costs) were conducted, adjusting for age, sex, and survival. Subgroup analyses were performed for patients with primary colorectal, lung, prostate, or breast cancer.

Results From 2002 to 2007, use of systemic therapy in the last 12–4 months of life increased by 21% (95% CI: 10% to 33%); no significant change in use in the last 3 months of life was observed. Costs for both periods increased over time, by 48% (95% CI: 36% to 63%) and by 33% (95% CI: 19% to 49%) respectively. The trends varied across cancer sites, with the greatest increases being observed for lung and colorectal cancer patients.

Conclusions The use and costs of systemic therapy have generally been increasing, putting pressure on health care providers and payers, but the quality-of-life implications for patients must be better understood.

Key Words Systemic therapy, chemotherapy, costs, end-of-life care, palliative care

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INTRODUCTION

Care for cancer patients near the end of life has two major goals: extending life and managing symptoms to maintain quality of life[1]. The potential survival benefit of anticancer therapy (including conventional chemotherapy, hormone therapy, and targeted therapy—collectively referred to as "systemic therapy" hereafter) for patients with advanced disease is modest, especially in later lines of therapy toward the end of life, and statistically significant improvements observed in clinical trials are not necessarily clinically significant[2]. Likewise, the use of progression-free survival as the primary outcome in clinical trials in this setting might not, in practice, translate to meaningful benefits for patients in terms of quantity or quality of life[1,3]. Modest gains must be balanced against the risk of toxicities associated with the therapy. A meta-analysis of phase III clinical trials found, in advanced cancer, significantly higher odds of severe toxicities, toxicity-related treatment discontinuation, and toxic death for newly-approved drugs than for their comparators[4]. For targeted therapies directed to biomarker-selected patient populations, the benefits are relatively greater and harms are lessened[5,6], but the trade-offs between quantity and quality of life remain.

Clinical guidelines recommend that need for palliative care—including, but not limited to, symptom control, psychosocial support, and advance care planning—be assessed for patients throughout the course of their disease[7,8].

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It has been recognized that palliative care should not be limited to the end-of-life setting and that such care can be provided early in the course of disease, concurrently with anticancer care[9]. However, little guidance has been developed about when and under what conditions a transition to care with primarily palliative intent should occur. For example, in advanced non-small-cell lung cancer, use of chemotherapy was found to extend survival, but its use in the last 2 weeks of life provided no additional benefit and was associated with decreased hospice use[10]. The overuse of aggressive care near death (including use of systemic therapy and admission to an intensive care unit or repeated emergency room visits) and the underuse of supportive care (including palliative home care, physician home visits, or admission to hospice) are indicators of poor quality of care at the end of life[11–13]. Comparisons across Canadian regions show that between 2% and 7% of patients are admitted to the intensive care unit very near the end of life and that 32%–67% receive palliative home nursing in the last 6 months of life[14]. After adjustments for patient and disease characteristics, significant unexplained regional variation in such quality indicators has been observed[12,14], indicating wide variation in practice.

Published evidence also suggests that the care of cancer patients near the end of life has been becoming more aggressive over time: aggregate indicators of aggressiveness reportedly increased 6% per year in the United States[12] and 1% per year in Canada[15]. Recently approved drugs for advanced cancer have demonstrated increased toxicity independent of clinical effectiveness[4], suggesting that the balance of harms to benefits might be worsening. The price of new drugs for advanced cancer has also been increasing rapidly, at approximately 12% per year from 1995 to 2013, despite the fact that the survival benefit with the newer drugs is no better than with the older ones[16]. Taken together, the increase in aggressive care, the greater risks of toxicity, and the increasing cost of drugs for advanced disease indicate a need to better characterize trends in the use and costs of systemic therapy near the end of life. The scale of the issue has to be understood, in terms of both the number of patients affected and the costs incurred. The objective of the present study was therefore to use population-based administrative data to understand trends in the use and costs of systemic therapy for patients in the last year of life.

METHODS

The study used a retrospective cohort design, in which the cohort consisted of all adult patients who died of malignant neoplasms (*International Classification of Diseases* version 10 codes C00–C97 for underlying cause of death) between 1 January 2002 and 31 December 2007. The cohort was defined using data from the BC Cancer Registry, a registry of all cancer diagnoses in British Columbia, including data about disease characteristics, patient demographics, and mortality. The study cohort was limited to patients who had been diagnosed fewer than 5 years but more than 3 months before death and those who were at least 19 years of age at diagnosis.

Using the unique provincial health insurance numbers for the patients, the BC Cancer Registry data were linked to pharmacy dispensing records from the province's Systemic Therapy Program to obtain prescription dates, drug names, and costs. The Systemic Therapy Program is the sole public provider of systemic anticancer therapy to cancer patients in British Columbia; consequently the program's dispensing records provide population-based data on systemic therapy use and cost.

Any dispensing record for a systemic therapy drug was used as an indicator variable, and the total cost for systemic therapy was calculated from the ingredient costs of the dispensed drugs for two periods: the last 12–4 months of life and the last 3 months of life. Those two periods are consistent with differences in practice and in health services use as patients approach the end of life[17]. For patients diagnosed less than 1 year before death, costs were calculated from the diagnosis date onward. All costs were expressed in 2009 Canadian dollars, using the health care component of Statistics Canada's Consumer Price Index[18]. Mean cost was calculated for the two time periods, and confidence intervals (CIs) were generated using nonparametric bootstrapping. In exploratory data analyses, average systemic therapy costs were calculated by month before death to understand the cost trajectory and to verify the choice of time periods. Frequency of systemic therapy use in the two periods was compared using a McNemar test, and independent two-sample t-tests and chi-square tests were used in bivariate analyses to compare the characteristics of systemic therapy users and nonusers in each period.

Changes in systemic therapy use over time were analyzed using multivariable logistic regression. Changes in mean costs (for systemic therapy users only) were analysed using generalized linear models with a log-link function and gamma distribution[19]. The dependent variable for the cost analysis was mean monthly cost per patient, to account for the varying period of observation for each patient. Models were constructed for both time periods for the full cohort (all cancers) and for each of the 4 most common primary cancer sites: lung, colon and rectum, female breast, and prostate. The independent variable of interest in all models, time, was defined as patient year of death. The relationships between the outcomes of interest and year were found to be nonlinear; thus, in the final models, year was included as a categorical variable, with 2002 being the reference year. Covariates included in all models were patient age at death, sex, and an indicator for patients who survived for less than 1 year after diagnosis, intended as a proxy for poor prognosis. The analysis was conducted in the SAS software application (version 9.2: SAS Institute, Cary, NC, U.S.A.).

RESULTS

Table I summarizes the characteristics of the patient cohort. Overall, significantly more patients received systemic therapy in the last 12–4 months of life (41.4%; 95% CI: 40.8% to 42.0%) than in the last 3 months of life (30.6%; 95% CI: 30.0% to 31.2%; $p < 0.0001$). In both periods, users of systemic therapy were younger, more likely to be women, and more likely to survive at least 1 year after diagnosis. Year of death was not associated with systemic therapy use in the last 3 months of life, but the association was significant for use in the last 12–4 months.

TABLE I Characteristics of patients receiving and not receiving chemotherapy in the last 12–4 months and last 3 months of life

Characteristic	All pts (*n*)	Chemotherapy use during ...									
		Last 12–4 months					Last 3 months				
		No		Yes		*p* Value[b]	No		Yes		*p* Value[b]
		(*n*)	(%)[a]	(*n*)	(%)[a]		(*n*)	(%)[a]	(*n*)	(%)[a]	
Patients	24,030	14,077	59	9953	41		16,670	69	7360	31	
Mean age (years)	68.0±13.0	71.5±11.9		63±12.8		<0.0001	70.1±12.5		63.2±12.9		<0.0001
Sex											
Women	11,120	6276	56	4844	44		7474	67	3646	33	
Men	12,910	7801	60	5109	40	<0.0001	9196	71	3714	29	<0.0001
Year of death											
2002	3906	2369	61	1537	39		2760	71	1146	29	
2003	3942	2379	60	1563	40		2744	70	1198	30	
2004	4060	2350	58	1710	42		2758	68	1302	32	
2005	3973	2308	58	1665	42		2762	70	1211	30	
2006	3968	2310	58	1658	42		2750	69	1218	31	
2007	4181	2361	56	1820	44	0.0008	2896	69	1285	31	0.2065
Cancer site at diagnosis											
Breast	1503	403	27	1100	73		629	42	874	58	
Colon and rectum	3281	1886	57	1395	43		2408	73	873	27	
Lung	6249	4344	70	1905	30		4892	78	1357	22	
Prostate	1538	705	46	833	54		999	65	539	35	
Others	11,459	6739	59	4720	41	<0.0001	7742	68	3717	32	<0.0001
Survival <1 year	10,607	7136	67	3471	33	<0.0001	7508	71	3099	29	0.0001

[a] Calculated for the row.
[b] Between-group differences were tested using t-tests (for age) and chi-square tests.

The exploratory analysis indicated that, for the full cohort, mean systemic therapy cost by month (Figure 1) was relatively constant for the last 12–4 months of life and then declined rapidly during the last 3 months of life, consistent with the time periods defined for the analysis.

Among users of systemic therapy, the unadjusted mean cost of that therapy in the last 12–4 months of life increased to $6102 (95% CI: $5685 to $6507) in 2007 from $4151 (95% CI: $3866 to $4460) in 2002 ($p = 0.001$ for trend, Figure 2). The largest increase, in both absolute and relative terms, occurred in colorectal cancer patients, whose costs more than doubled, to $12,618 (95% CI: $11,083 to $14,244) from $5895 (95% CI: $5027 to $6810; $p = 0.009$). By contrast, no change was observed for breast cancer patients ($p = 0.74$). In the last 3 months of life, the mean cost of systemic therapy for lung cancer patients increased to $2,262 (95% CI: $1951 to $2602) in 2007 from $829 (95% CI: $673 to $995) in 2002 ($p < 0.001$), but little change occurred during that period for breast, colorectal, or prostate cancer patients, or for the full cohort (Figure 3). Table II presents mean costs for all years.

Adjusting for age, sex, and survival (<1 year), overall use of systemic therapy in the last 12–4 months of life increased by 21% from 2002 to 2007 (odds ratio: 1.21; 95% CI: 1.10 to 1.33), with variation by cancer site (Table III). Among users of systemic therapy, the cost for that therapy in the last 12–4 months of life increased by 48% between 2002 and 2007 (relative cost: 1.48; 95% CI: 1.36 to 1.63; Table IV).

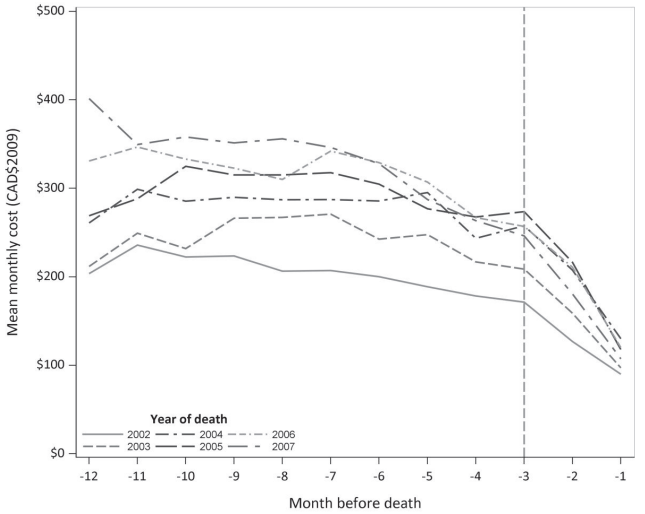

FIGURE 1 Mean monthly costs of systemic therapy for cancer decedents in British Columbia, 2002–2007, by month before death. The vertical dashed line marks the two time periods used in the analysis: the last 12–4 months of life, and the last 3 months of life.

Older age was associated with a lesser likelihood of using systemic therapy and lower relative costs over that period.

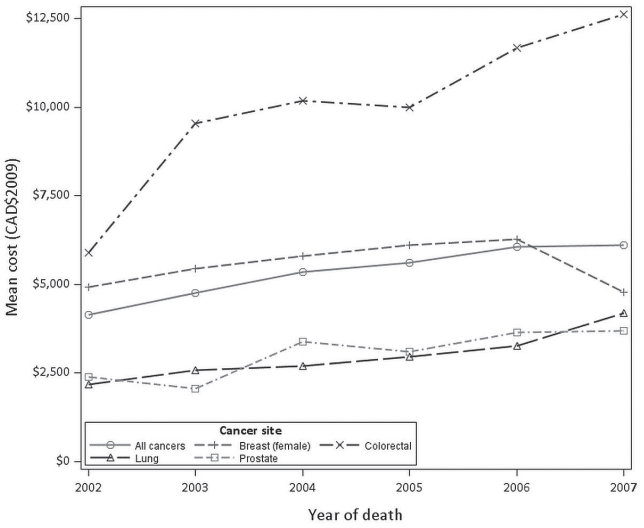

FIGURE 2 Mean systemic therapy costs for systemic therapy recipients in the last 12–4 months of life, overall and by cancer type, by year of death.

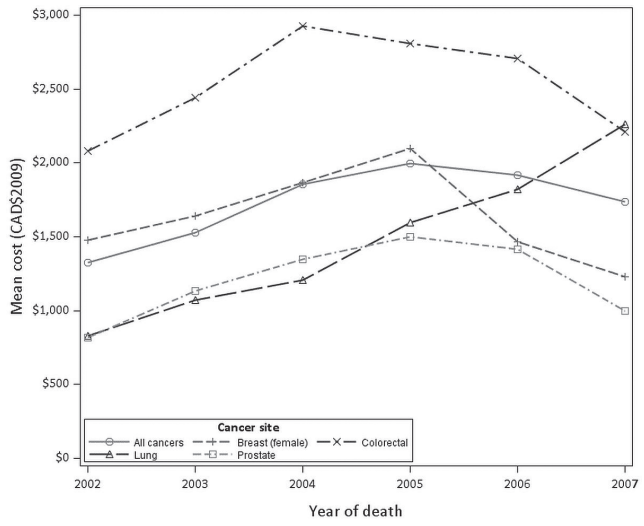

FIGURE 3 Mean systemic therapy cost for systemic therapy recipients in the last 3 months of life, overall and by cancer type, by year of death.

Patients who survived for less than 1 year were also less likely to receive systemic therapy and had lower therapy costs even after adjustment for observation time.

We observed a nonsignificant trend toward increased utilization of chemotherapy in the last 3 months of life (Table III). Of the four major cancer sites, only lung cancer showed a significant increase from 2002 to 2007 after adjustment for age, sex and survival (<1 year). The cost of chemotherapy in the last 3 months of life increased steadily over time for lung cancer patients, nearly tripling from 2002 to 2007 (relative cost: 2.72; 95% CI: 2.12 to 3.49; Table IV). By contrast, the cost of chemotherapy for the other cancer sites showed an inverted U relationship with time, with the highest relative costs in 2004 (breast cancer) and 2005 (colorectal and prostate cancer).

DISCUSSION

In British Columbia, both the use and the cost of systemic therapy increased over time for cancer patients in the last year of life. Overall, from 2002 to 2007, the use of systemic therapy in the last 12–4 months before death increased by 21%, and the mean cost of that therapy among users increased by 48%. From 2002 to 2007, the cost in the last 3 months of life increased by 33%, although use was largely unchanged. Those results suggest that, although the use and mean cost of systemic therapy among users both contribute to overall growth, the cost per user is the larger driver of expenditures in this setting.

The overall growth in the use and cost of systemic therapy observed for the full cohort is largely attributable to the growth in its use and cost in lung and colorectal cancer patients. Together, those two cancer sites accounted for 40% of decedents in the cohort, and the cost of systemic therapy for those sites in the last year of life roughly doubled during the study period. Lung cancer in particular was the only site for which systemic therapy use and cost both increased in the last 3 months of life. Previous work by Temel *et al.*[20] found that most lung cancer patients receiving systemic therapy near the end of life were prescribed an oral epidermal growth factor tyrosine kinase inhibitor. In British Columbia, the first agent of that class, erlotinib, was introduced in late 2005[21]. The introduction of erlotinib during the study period likely increased both the use of systemic therapy in lung cancer patients (because of ease of administration and a favourable toxicity profile[22]) and the cost. Our observation period was also a period of significant change in the management of metastatic colorectal cancer, with the introduction of irinotecan, oxaliplatin, and capecitabine for that indication in 2002[23] and of bevacizumab, the first targeted therapy for colorectal cancer, in 2006[24]. The availability of multiple new treatment options and their relatively higher costs[25,26] are likely the main drivers behind the growth observed in our study.

An exception to the observed growth occurred with respect to the cost in the last 3 months of life for breast, colorectal, and prostate cancers, whose relative costs were highest in 2004 and 2005. That pattern likely reflects a number of changes that occurred after that time. Generic irinotecan and generic bicalutamide, used in colorectal cancer and prostate cancer respectively, became available in 2006[27], contributing to reduced costs later in the observation period. However, that reduction was likely obscured in the last 12–4 months of life by increases in expenditures on high-cost drugs such as first-line bevacizumab, which was approved in 2006[24]. In breast cancer, the decline in costs might be attributable to less trastuzumab and docetaxel use in the last 3 months of life, because that combination became available as a first-line treatment option in mid-2005[28]. These examples of simultaneous treatment protocol, formulary, and pricing changes highlight the need to understand the policy context in which trends are observed.

The results of the present study add to the evidence that the use of systemic therapy in cancer patients toward the end of life has been growing and that the cost of systemic therapy is increasing. The expansion of systemic therapy

TABLE II Mean drug costs for patients receiving chemotherapy in the last 12–4 months and last 3 months of life, by year of death and cancer site

Cancer site	Year	Systemic chemotherapy during ...							
		Last 12–4 months				Last 3 months			
		Pts (*n*)	Costs (2009 CA$)		*p* Value (trend)	Pts (*n*)	Costs (2009 CA$)		*p* Value (trend)
			Mean	95% CI			Mean	95% CI	
Breast	2002	189	4,934	3,889 to 6,091		150	1,480	1,148 to 1,871	
	2003	220	5,444	4,309 to 6,628		160	1,641	1,322 to 2,027	
	2004	176	5,807	4,565 to 7,160		141	1,865	1,407 to 2,341	
	2005	162	6,106	4,659 to 7,661		136	2,097	1,612 to 2,628	
	2006	167	6,271	5,093 to 7,477		136	1,467	1,114 to 1,866	
	2007	186	4,780	3,754 to 5,976	0.74	151	1,231	991 to 1,503	0.61
Colon and rectum	2002	221	5,895	5,027 to 6,810		123	2,082	1,607 to 2,604	
	2003	217	9,545	8,435 to 10,674		154	2,443	2,062 to 2,864	
	2004	235	10,189	9,049 to 11,339		150	2,927	2,476 to 3,424	
	2005	248	9,990	8,950 to 11,068		163	2,808	2,371 to 3,241	
	2006	208	11,675	10,138 to 13,324		129	2,705	2,200 to 3,264	
	2007	266	12,618	11,083 to 14,244	0.009	154	2,210	1,751 to 2,700	0.67
Lung	2002	266	2,183	1,889 to 2,540		194	829	673 to 995	
	2003	257	2,590	2,251 to 2,968		195	1,073	877 to 1,274	
	2004	322	2,696	2,326 to 3,071		250	1,207	1,024 to 1,414	
	2005	347	2,959	2,554 to 3,410		221	1,596	1,330 to 1,898	
	2006	336	3,276	2,802 to 3,741		241	1,821	1,553 to 2,101	
	2007	377	4,182	3,649 to 4,730	0.004	256	2,262	1,951 to 2,602	0.0002
Prostate	2002	128	2,390	1,749 to 3,137		80	816	643 to 1,004	
	2003	114	2,052	1,590 to 2,565		85	1,132	630 to 2,031	
	2004	140	3,389	2,113 to 5,392		92	1,348	994 to 1,764	
	2005	125	3,113	2,311 to 4,063		75	1,500	1,088 to 2,011	
	2006	164	3,639	3,055 to 4,307		103	1,416	1,077 to 1,797	
	2007	162	3,706	2,981 to 4,581	0.025	104	1,000	731 to 1,315	0.45
Overall	2002	1,537	4,151	3,866 to 4,460		1,146	1,324	1,213 to 1,444	
	2003	1,563	4,768	4,443 to 5,122		1,198	1,530	1,418 to 1,654	
	2004	1,710	5,342	4,977 to 5,695		1,302	1,857	1,692 to 2,037	
	2005	1,665	5,618	5,236 to 5,990		1,211	1,994	1,835 to 2,170	
	2006	1,658	6,070	5,699 to 6,487		1,218	1,915	1,756 to 2,079	
	2007	1,820	6,102	5,685 to 6,507	0.001	1,285	1,739	1,601 to 1,889	0.12

Pts = patients; CI = confidence interval.

in this context is a product of complex upstream factors, including patient and provider expectations[29], and the resulting rising expenditures on systemic therapy drugs is increasing the pressure on public and private providers alike to control costs[18]. However, the implications of the trends with respect to patient outcomes and quality of care are not clear. The initiation of new anticancer therapies in the last month of life and the continuation of ongoing therapy in the last 2 weeks of life are indicators for poor quality of care, and both have been increasing over time[30]; however, little evidence is available about the appropriateness of the earlier use of systemic therapy in this setting. Although systemic therapy can extend survival and might be underused in settings in which its effectiveness has been demonstrated[31], other evidence suggests that use is inappropriately high in patients with cancers known to be unresponsive to chemotherapy[32].

Regardless of the uncertainty concerning the correct level of chemotherapy use for high-quality patient care in the last year of life, mounting evidence supports the value of early palliative care in this setting. A review conducted by the American Society of Clinical Oncology found that, although many studies of palliative care interventions were not comparable because of variation in the services provided, all such interventions provided patients with some improvement in quality of life, symptoms, or satisfaction with care, in the absence of evidence of harm or increased cost[33]. A randomized controlled trial of early palliative care in metastatic lung cancer patients found not only a reduction in chemotherapy use in the last 2 months of life,

TABLE III Results of multiple logistic regression for any systemic therapy use in the last 12–4 months and last 3 months of life, for all cancers and by cancer site

Variable	Comparator	Systemic therapy use by cancer site									
		Overall		Breast		Colon/rectum		Lung		Prostate	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Last 12–4 months of life											
Age at death (continuous)	Per year	0.95	0.95 to 0.95	0.96	0.95 to 0.97	0.93	0.92 to 0.93	0.93	0.93 to 0.94	0.96	0.95 to 0.97
Sex (reference: men)	Women	1.18	1.12 to 1.24			0.85	0.73 to 1.00	0.99	0.88 to 1.11		
Year of death (reference: 2002)	2003	1.00	0.91 to 1.11	1.55	1.03 to 2.35	0.96	0.73 to 1.26	0.96	0.78 to 1.19	1.13	0.79 to 1.63
	2004	1.12	1.02 to 1.23	1.05	0.70 to 1.57	1.11	0.85 to 1.45	1.30	1.06 to 1.59	1.27	0.90 to 1.80
	2005	1.13	1.03 to 1.25	0.99	0.65 to 1.51	1.16	0.89 to 1.51	1.42	1.16 to 1.74	1.25	0.87 to 1.79
	2006	1.13	1.03 to 1.25	0.98	0.65 to 1.47	1.03	0.78 to 1.35	1.34	1.09 to 1.64	1.84	1.29 to 2.62
	2007	1.21	1.10 to 1.33	1.11	0.74 to 1.68	1.37	1.05 to 1.79	1.57	1.29 to 1.92	1.40	0.99 to 1.96
Survival (reference: ≥1 year)	<1 Year	0.50	0.48 to 0.53	0.50	0.37 to 0.68	0.48	0.40 to 0.57	0.76	0.67 to 0.85	1.25	0.94 to 1.66
Last 3 months of life											
Age at death (continuous)	Per year	0.96	0.96 to 0.96	0.97	0.96 to 0.98	0.95	0.95 to 0.96	0.95	0.94 to 0.95	0.97	0.96 to 0.98
Sex (reference: men)	Women	1.20	1.13 to 1.27			0.84	0.72 to 1.00	1.08	0.96 to 1.23		
Year of death (reference: 2002)	2003	1.04	0.94 to 1.15	1.01	0.71 to 1.43	1.33	1.00 to 1.76	1.00	0.80 to 1.26	1.43	0.98 to 2.09
	2004	1.14	1.03 to 1.25	1.04	0.73 to 1.50	1.27	0.95 to 1.69	1.36	1.09 to 1.69	1.28	0.89 to 1.85
	2005	1.06	0.96 to 1.17	1.14	0.79 to 1.66	1.37	1.04 to 1.82	1.10	0.88 to 1.38	1.10	0.75 to 1.61
	2006	1.08	0.98 to 1.19	1.03	0.72 to 1.49	1.17	0.87 to 1.57	1.25	1.00 to 1.55	1.53	1.06 to 2.20
	2007	1.08	0.98 to 1.19	1.12	0.78 to 1.61	1.31	0.99 to 1.75	1.32	1.07 to 1.65	1.30	0.91 to 1.87
Survival (reference: ≥1 year)	<1 Year	0.91	0.86 to 0.97	0.88	0.66 to 1.17	1.41	1.18 to 1.67	1.31	1.15 to 1.49	1.52	1.15 to 2.02

OR = odds ratio; CI = confidence interval.

TABLE IV Results of generalized linear regression for chemotherapy costs in the last 12–4 months and last 3 months of life, for all cancers and by cancer site

Variable	Comparator	Relative cost for systemic therapy by cancer site									
		Overall		Breast		Colorectal		Lung		Prostate	
		Relative cost	95% CI	Relative cost	95% CI	Relative cost	95% CI	Relative cost	95% CI	Relative cost	95% CI
Last 12–4 months of life											
Age at death (continuous)	Per year	0.98	0.98 to 0.98	0.96	0.95 to 0.96	0.97	0.96 to 0.98	0.98	0.98 to 0.99	0.98	0.97 to 0.99
Sex (reference: men)	Women	0.85	0.81 to 0.90			0.72	0.63 to 0.82	0.91	0.82 to 1.02		
Year of death (reference: 2002)	2003	1.12	1.02 to 1.24	1.21	0.92 to 1.57	1.61	1.29 to 2.00	1.25	1.03 to 1.53	0.84	0.60 to 1.18
	2004	1.30	1.18 to 1.42	1.29	0.97 to 1.71	1.72	1.39 to 2.13	1.28	1.06 to 1.54	1.47	1.07 to 2.02
	2005	1.36	1.24 to 1.50	1.25	0.94 to 1.67	1.81	1.46 to 2.24	1.43	1.19 to 1.72	1.23	0.88 to 1.70
	2006	1.48	1.35 to 1.63	1.77	1.32 to 2.36	2.02	1.62 to 2.52	1.58	1.31 to 1.91	1.41	1.03 to 1.91
	2007	1.48	1.36 to 1.63	1.23	0.93 to 1.63	2.16	1.76 to 2.66	1.90	1.58 to 2.28	1.45	1.07 to 1.98
Survival (reference: ≥1 year)	<1 Year	0.86	0.81 to 0.91	0.70	0.55 to 0.90	0.91	0.79 to 1.06	0.65	0.58 to 0.72	0.84	0.66 to 1.07
Last 3 months of life											
Age at death (continuous)	Per year	0.99	0.98 to 0.99	0.97	0.97 to 0.98	0.97	0.97 to 0.98	0.98	0.97 to 0.98	0.99	0.97 to 1.00
Sex (reference: men)	Women	0.82	0.77 to 0.87			0.74	0.63 to 0.87	0.86	0.74 to 0.99		
Year of death (reference: 2002)	2003	1.15	1.03 to 1.29	1.15	0.87 to 1.53	1.11	0.83 to 1.49	1.33	1.02 to 1.73	1.44	0.97 to 2.14
	2004	1.41	1.27 to 1.58	1.41	1.05 to 1.88	1.34	1.00 to 1.80	1.48	1.15 to 1.90	1.62	1.10 to 2.40
	2005	1.52	1.36 to 1.70	1.36	1.02 to 1.82	1.41	1.06 to 1.88	2.06	1.59 to 2.66	1.74	1.15 to 2.62
	2006	1.47	1.32 to 1.65	1.16	0.86 to 1.55	1.38	1.02 to 1.88	2.19	1.71 to 2.82	1.65	1.13 to 2.41
	2007	1.33	1.19 to 1.49	0.89	0.67 to 1.19	1.06	0.79 to 1.42	2.72	2.12 to 3.49	1.16	0.80 to 1.70
Survival (reference: ≥1 year)	<1 Year	0.84	0.79 to 0.90	1.08	0.85 to 1.38	1.02	0.86 to 1.21	0.60	0.52 to 0.70	0.69	0.52 to 0.91

earlier admission to hospice, and improved quality of life, but also improved survival[34,35]. Furthermore, no difference was observed in the number of lines of chemotherapy provided in the early-palliative-care and standard-care arms, nor any difference in time to progression between the lines of chemotherapy, suggesting that anticancer care and palliative care can be effectively delivered simultaneously[35]. Providing standard cancer care, including systemic therapy, together with early palliative care appears to provide both quantity and quality of life to patients with advanced disease. A recent population-based study of cancer decedents in Ontario reported that health care costs in the last month of life were reduced in patients who received palliative care services in the last year of life, even if those patients went on to receive aggressive end-of-life care[36]. On average, median costs were $536 higher in recipients of systemic therapy in the last 14 days of life than in patients who did not receive such aggressive care, and early palliative care was independently associated with a $418 decrease in median cost[36]. Those results suggest that, even without changing the aggressiveness of care at end of life, early palliative services can to some extent offset the additional costs.

Our study was not designed to address the question of appropriateness of chemotherapy use toward the end of life, but the results imply that the intensity of care in the last 3 months of life has generally been increasing for cancer patients, with the exception of lung cancer patients. The results of the multivariable analysis also indicated that chemotherapy use and cost were lower for older patients and patients with poor survival, suggesting that older patients who might not tolerate chemotherapy well or poor-prognosis patients who might not benefit are less likely to receive anticancer therapy. The associations between chemotherapy use and age[31,37,38] or survival[38,39] have been previously described in the literature. However, the association with survival time should be interpreted with some caution. The expectation would be that use of systemic therapy increases survival in this setting, and so the association between the indicator for survival (<1 year), intended as a proxy for poor prognosis, and use of systemic therapy might arise in part from reverse causality. This indicator was included to adjust for confounding in the trend analysis, not to achieve an unbiased estimate of the relationship between survival and systemic therapy use. However, our findings are consistent with prior studies and raise important questions for potential future research into the appropriateness of care. Adjusting for stage at diagnosis or time to local or distant progression could also potentially control for differences in prognosis or disease trajectory, providing additional insight into the appropriateness of the observed systemic therapy use. Unfortunately, those variables were not available in the study dataset, but should be considered for future analyses.

The limited availability of patient and disease characteristics in the administrative data used in our study restricted the scope of the analysis. For example, increasing comorbidity is associated with less systemic therapy use[31,37,38], but whether comorbidity confounds the relationship between systemic therapy use and trends over time is unclear. A growing body of evidence also suggests that the use of systemic therapy varies across care providers, care settings, and regions[12,32,37,38,40]. A limitation of the present study is that it does not take into account the broader contextual factors that are associated with treatment intensity[41] and that might be associated with the observed increase in systemic therapy use and cost over time. A further limitation is the age of the data used in the analysis. The reported increase in systemic therapy cost has likely continued and might have accelerated in the intervening time. Since 2007, many new drugs for metastatic cancer have been introduced, and the prices of those drugs have been increasing over time, independent of their effect on survival[16,18]. Finally, our analysis considered only the cost of systemic therapy; it did not take into account other health system costs, patient out-of-pocket costs, or indirect costs that might be affected by changes in systemic therapy use. Compared with patients who do not receive systemic therapy as they approach death, those receiving systemic therapy in the last 14 days of life have higher acute care costs and lower home and community care costs[36], suggesting that the effect on health system costs extends beyond the systemic therapy budget.

The major strength of our study is its use of population-based cancer registry and systemic therapy program data for the province of British Columbia, allowing for a comprehensive understanding of systemic therapy use and cost. The BC Cancer Registry captured 91% of the cancer cases in the province over the study period[42], and dispensing records from the Systemic Therapy Program included all systemic therapy covered through the province's universal public health care system. Those data are an invaluable resource for secondary analysis and are well-suited to work of the present scope.

CONCLUSIONS

Both the use and the costs of systemic therapy for cancer patients in the last year of life have been increasing, but more work is needed to understand the extent to which that increase is appropriate or not, and whether the rising expenditure is providing value to patients and health care systems. Early palliative care can maintain quality of life for patients and can be delivered concurrently with anticancer therapy, but an understanding of the relationship between increased systemic therapy use and the uptake of palliative care is necessary to understand the ultimate effect on care and quality of life for patients approaching death.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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