Use of Palliative Chemotherapy for Advanced Bladder Cancer: Patterns of Care in Routine Clinical Practice

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Abstract

Background: Palliative chemotherapy for advanced bladder cancer is recommended in clinical practice guidelines. Patterns of care in routine clinical practice have not been well described. This article describes use rates of chemotherapy and referral rates to medical oncology in the last year of life among patients who have died of bladder cancer. **Methods:** A population-based cohort of patients with bladder cancer was identified from the Ontario Cancer Registry; the study population included patients who died of bladder cancer between 1995 and 2009. Electronic records of treatment and physician billing records were used to identify treatment patterns and referral to medical oncology. Log-binomial and modified Poisson regression were used to examine factors associated with chemotherapy use and medical oncology consultation. **Results:** A total of 8,005 patients died of bladder cancer, 25% (n=1,964) of whom received chemotherapy in the last year of life. Use was independently associated with patient age, comorbidities, socioeconomic status, sex, time period, and treatment region. A total of 68% (n=5,426) of patients were seen by a medical oncologist. Referral to medical oncology was associated with age, comorbidities, year of death. Geographic variation was seen with chemotherapy use—from 18% to 30%—that persisted on adjusted analysis. **Conclusions:** The efficacy of palliative chemotherapy demonstrated in clinical trials and recommended in guidelines has not translated into widespread use in practice. Understanding the extent to which patient preferences and health system factors influence use is needed. Access to acceptable palliative systemic treatments remains an unmet need for most patients dying of bladder cancer.

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Background

With approximately 75,000 new diagnoses and 15,000 deaths each year in the United States, bladder cancer is the sixth most common cancer and eighth leading cause of cancer death. Approximately 30% of patients with bladder cancer will present with advanced disease or develop metastatic disease after presentation.[1]

For patients with advanced disease, clinical trials suggest that multiagent cisplatin-based chemotherapy is associated with improved survival. Regimens studied include methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC), dose-dense MVAC (ddMVAC), and gemcitabine/cisplatin (Gem/Cis).[2–4] On this basis, internationally recognized guidelines recommend cisplatin-based combination chemotherapy for fit patients with metastatic bladder cancer.[5–8]

Although clinical trials have established the efficacy of MVAC and Gem/Cis, limited data are available regarding their use in routine clinical practice. Use encompasses several aspects of care, including access to

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care, appropriateness of therapy, and patient values, such as willingness to accept treatment.[9,10] We have recently described referral patterns to medical oncology and subsequent use of perioperative chemotherapy among patients treated with cystectomy.[11] In 2009, Porter et al[12] used SEER-Medicare data to describe the use of chemotherapy among all patients with bladder cancer. They found that chemotherapy use was 13% among those initially diagnosed with stage I cancer, 28% for those initially diagnosed with stage II, 37% for stage III, and 57% for stage IV. This study did not explicitly describe use of palliative chemotherapy, because the stage groupings in their analysis were based only on stage at time of diagnosis. To our knowledge, no studies address use of chemotherapy in the palliative setting at the population level. The purpose of this study is to describe use of palliative chemotherapy for bladder cancer and patterns of referral to medical oncology.

Methods

Study Design and Population

This was a population-based, retrospective cohort study of all patients who died of bladder cancer in the Canadian province of Ontario. Ontario has a population of approximately 13.5 million and a single-payer universal health insurance program. All incident cases of bladder cancer in 1984 through 2009 were identified using the Ontario Cancer Registry (OCR) and linked treatment records; the study population included all of these patients who died of bladder cancer between 1995 and 2009.

Data Sources

The OCR is a passive, population-based cancer registry that captures diagnostic and demographic information on at least 98% of all incident cases of cancer in the province of Ontario.[13,14] A variety of electronic administrative health databases were linked to the OCR. Records of hospitalization from the Canadian Institute for Health Information (CIHI) provided information about surgical interventions; these records are known to be consistent and complete.[15] Provincial physician billing records, treatment records from regional cancer centers, and treatment records from Ontario's chemotherapy reimbursement program were used to identify chemotherapy use.

Identifying Patients Who Died of Bladder Cancer

Vital status was available up to December 31, 2012, and cause of death was available within the OCR up to December 31, 2010. Patients were excluded if they did not die between 1995 and 2009, or had a nonmalignant cause of death. Patients were also excluded if they had multiple malignancies and the cause of death aligned or possibly aligned with a separate malignancy from bladder cancer. Patients who only had bladder and prostate cancer in the registry but who died of malignancy not otherwise specified were considered to have died of bladder cancer.

Definitions of Measures and Outcomes

Comorbidity was classified using the modified Charlson index,[16] and was calculated from the administrative data from hospital admission records for the 5-year period before death, excluding malignancy.[17] Age used was the age at death, given the inability to ascertain age at which recurrent or metastatic disease occurred. Socioeconomic status (SES) was derived from postal code of residence at the time of diagnosis, and was divided into quintiles or median household income, as previously described. Quintile 1 represents the communities where the fiscally poorest 20% of the Ontario population resided.[18]

The first general hospital attended by the patient within 30 days before or after diagnosis was designated the diagnosing hospital. If the patient did not attend a general hospital, the hospital that reported the diagnosis to OCR was designated the diagnosing hospital. If the patient attended multiple hospitals, the institution where the patient was seen immediately before the diagnosis was considered the diagnosing hospital. The diagnosing hospitals were then divided into quartiles based on total volume of patients seen. The geographic regions evaluated reflect the catchment areas for Ontario's regional cancer centers. Each case in the current study was assigned to one of these geographic regions based on their Ministry of Health residence code.[18]

Outcomes included the delivery of palliative chemotherapy and referral to a medical oncologist. Because there is no single administrative data source that allows identification of medical oncologists in Ontario, a proxy measure of medical oncologists was used consisting of physicians who submitted billing records for adjuvant, neoadjuvant, or palliative use of chemotherapy between 1995 and 2009. We have used a similar approach elsewhere.[19] Each case was

considered to have been seen by a medical oncologist in the 12 months before death if any of these physicians submitted visit billing codes during this period. Palliative chemotherapy was defined as any chemotherapy received in the last 12 months of life. A look-back approach from death was used to determine palliative chemotherapy. This approach was needed given the uncertainty of the number of patients with bladder cancer who developed advanced disease and has been used previously for palliative radiation.[20]

Statistical Analysis

To describe temporal trends, the study population was divided into 3 study periods of death: 1995 to 1999, 2000 to 2004, and 2005 to 2009. Factors associated with chemotherapy use and with seeing a medical oncologist were evaluated by log-binomial regression models. Modified Poisson regression with a robust error variance was used when the log-binomial regression failed to converge. Results were considered statistically significant at a *P* value of less than 0.05. All analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC).

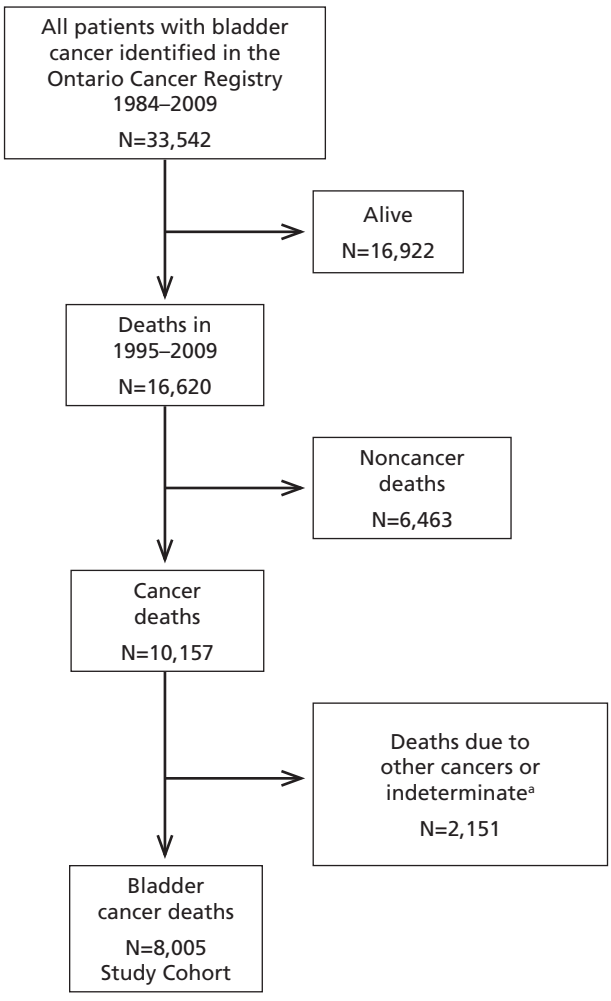

Figure 1. Patient flow diagram for identifying bladder cancer deaths.
[a]Cases with >1 cancer diagnoses and a cause of death probably related to that cancer.

Results

Study Population

We identified 8,005 patients who died of bladder cancer in Ontario between 1995 and 2009 (Figure 1). Table 1 shows the characteristics of these 8,005 patients; notably, only 39% (n=3,146) had previously received radical-intent surgery or radiation-therapy. The advanced age (75% were >70 years) and sex distribution (73% were male) were notable.

Table 1. Characteristics of Patients Who Died of Bladder Cancer in Ontario (1995–2009)

	All Patients (N=8,005)
Previous radical therapy	
Surgery	2,409 (30%)
Radiation	737 (9%)
None	4,859 (61%)
Year of death	
1995–1999	2,199 (27%)
2000–2004	2,749 (34%)
2005–2009	3,057 (38%)
Patient-related factors	
Age, y	
20–49	179 (2%)
50–59	500 (6%)
60–69	1,280 (16%)
70–79	2,739 (34%)
≥80	3,307 (41%)
Sex	
Male	5,811 (73%)
Female	2,194 (27%)
Socioeconomic status[a]	
Q1	1,759 (22%)
Q2	1,843 (23%)
Q3	1,686 (21%)
Q4	1,410 (18%)
Q5	1,298 (16%)
Comorbidity score	
0	2,949 (37%)
1–2	3,145 (39%)
≥3	1,911 (24%)

Abbreviation: Q, quintile.
[a]Socioeconomic status data were not available for 9 patients.

Use of Palliative Chemotherapy

A modest increase was seen in use of palliative chemotherapy over the study periods, from 22% to 26%. Factors associated with use of palliative chemotherapy are shown in Table 2. Patients with older age and greater comorbidity were less likely to receive treatment, as were women and patients from lower SES communities. We also observed some geographic variation in use of palliative chemotherapy (range, 18%–30%). These findings persisted on adjusted analyses ($P<.05$). Hospital volume of bladder cancer cases was associated with a statistically significant variation in use of palliative chemotherapy. However, there was no clear association with a higher volume being associated with an increased likelihood of palliative chemotherapy use.

Referral to Medical Oncology

A total of 68% of patients (5,426 of 8,005) were seen by a medical oncologist during the last 12 months of life. Factors associated with seeing a medical oncologist and with receiving chemotherapy for those who saw a medical oncologist are shown in Table 3. Age, sex, comorbidities, SES, and region were associated with seeing a medical oncologist in the last 12 months of life. There was also a very modest increase over time, from 66% to 69%. Geographic variation in referral patterns (range, 57%–79%) persisted on adjusted analyses. There was again a statistically significant association between hospital bladder cancer volume and referral patterns or use of chemotherapy, but not in a dose-dependent fashion (ie, the highest rate of referral occurred in the second lowest quartile of hospital volume).

Chemotherapy Regimens

Drug regimens were available for 977 of 1,964 of patients (50%) who received chemotherapy in the last year of life (Table 4). Use of Gem/Cis (1%, 30%, 40%) and gemcitabine/carboplatin (Gem/Carbo; 0%, 11%, 24%) increased over the 3 study periods (1995–1999, 2000–2004, 2005–2009, respectively); use of MVAC (21%, 8%, 2%) decreased over the study periods.

Discussion

Based on the results of clinical trials, palliative chemotherapy is recommended in treatment guidelines[5,6,8] as an option for appropriate patients with advanced bladder cancer. In this population-based study, we explored use and referral patterns for a cohort of patients who died of bladder cancer in Ontario between 1995 and 2009. Only 25% of these patients were treated with palliative chemotherapy. In the most current

Table 2. Factors Associated With Receiving Chemotherapy in the Last 12 Months of Life (N=8,005)[a]

Characteristic	Proportion Treated With Chemotherapy (N=1,964)	Multivariate Analyses[b]
RR (95% CI)	*P* Value	
Patient-related		
Year of death		<.001
1995–1999 (n=2,199)	22%	Ref
2000–2004 (n=2,749)	25%	1.14 (1.04–1.24)
2005–2009 (n=3,057)	26%	1.21 (1.11–1.32)
Sex		.012
Male (n=5,811)	26%	Ref
Female (n=2,194)	22%	0.91 (0.84–0.98)
Age, y		<.001
20–49 (n=179)	61%	Ref
50–59 (n=500)	59%	0.98 (0.87–1.11)
60–69 (n=1,280)	45%	0.80 (0.71–0.90)
70–79 (n=2,739)	26%	0.49 (0.43–0.55)
≥80 (n=3,307)	8%	0.15 (0.13–0.18)
Socioeconomic status[c]		.01
Q1 (n=1,759)	21%	0.84 (0.75–0.94)
Q2 (n=1,843)	24%	0.89 (0.80–0.98)
Q3 (n=1,686)	24%	0.89 (0.80–0.99)
Q4 (n=1,410)	27%	0.98 (0.89–1.09)
Q5 (n=1,298)	28%	Ref
Charlson comorbidity score		<.001
0 (n=2,949)	33%	Ref
1–2 (n=3,145)	22%	0.82 (0.76–0.89)
≥3 (n=1,911)	16%	0.61 (0.54–0.68)
System-related		
Region		<.001
1 (n=3,366)	26%	Ref
2 (n=1,148)	18%	0.72 (0.63–0.81)
3 (n=774)	28%	0.98 (0.88–1.09)
4 (n=504)	21%	0.85 (0.72–1.01)
5 (n=155)	27%	0.97 (0.76–1.23)
6 (n=267)	21%	0.77 (0.62–0.96)
7 (n=640)	18%	0.73 (0.62–0.86)
8 (n=1,138)	30%	1.16 (1.06–1.28)
Hospital volume[d]		.019
Q1 (n=2,224)	25%	0.99 (0.90–1.10)
Q2 (n=1,772)	26%	1.09 (0.99–1.21)
Q3 (n=2,134)	24%	0.93 (0.84–1.04)
Q4 (n=1,792)	23%	Ref

Abbreviations: Q, quintile; ref, referent; RR, relative risk, SES, socioeconomic status.
[a]SES, region, and hospital volume were missing for 101 of 8,005 of cases (1%). These patients have been removed from the analysis.
[b]Log-binomial regression was used to estimate RRs.
[c]SES is reported by quintile. Q1 represents the lowest SES group.
[d]Q4 represents highest hospital volume.

Table 3. Variables Associated With Having Seen a Medical Oncologist and Receiving Chemotherapy Within 12 Months of Death From Bladder Cancer[a]

	Factors Associated With Seeing Medical Oncology in the Last Year of Life			Factors Associated With Receiving Chemotherapy in the Last Year of Life for Those Who Saw Medical Oncology		
	Proportion	Multivariate Analyses[b]		Proportion	Multivariate Analyses[c]	
Characteristic	(N=5,426)	RR (95% CI)	*P* Value	(N=1,958)	RR (95% CI)	*P* Value
Patient-related						
Year of death			.006			<.001
1995–1999	66%	Ref		33%	Ref	
2000–2004	68%	1.03 (0.99–1.07)		37%	1.10 (1.01–1.20)	
2005–2009	69%	1.06 (1.02–1.10)		38%	1.17 (1.09–1.28)	
Sex			.023			.043
Male	69%	Ref		37%	Ref	
Female	65%	0.96 (0.93–0.99)		33%	0.93 (0.86–1.00)	
Age, y			<.001			<.001
20–49	92%	Ref		67%	Ref	
50–59	87%	0.95 (0.90–1.00)		68%	1.02 (0.91–1.15)	
60–69	85%	0.93 (0.89–0.98)		53%	0.85 (0.76–0.95)	
70–79	74%	0.82 (0.78–0.86)		35%	0.59 (0.52–0.66)	
≥80	51%	0.57 (0.54–0.60)		16%	0.26 (0.23–0.31)	
SES, quintile[d]			<.001			.172
1	64%	0.90 (0.85–0.94)		33%	0.91 (0.82–1.00)	
2	67%	0.92 (0.88–0.97)		36%	0.95 (0.87–1.05)	
3	68%	0.95 (0.90–0.99)		35%	0.94 (0.85–1.04)	
4	69%	0.95 (0.91–1.00)		39%	1.02 (0.93–1.12)	
5	73%	Ref		38%	Ref	
Charlson comorbidity score			<.001			<.001
0	74%	Ref		45%	Ref	
1–2	65%	0.93 (0.90–0.96)		33%	0.85 (0.80–0.91)	
≥3	63%	0.90 (0.86–0.93)		25%	0.66 (0.59–0.73)	
System-related						
Region			<.001			<.001
1	72%	Ref		36%	Ref	
2	59%	0.82 (0.78–0.86)		30%	0.81 (0.72–0.92)	
3	64%	0.87 (0.83–0.92)		43%	1.04 (0.94–1.15)	
4	77%	1.11 (1.05–1.17)		27%	0.78 (0.67–0.93)	
5	79%	1.10 (1.00–1.21)		33%	0.94 (0.74–1.20)	
6	57%	0.78 (0.71–0.86)		37%	0.86 (0.71–1.06)	
7	57%	0.82 (0.76–0.87)		31%	0.82 (0.71–0.96)	
8	68%	0.98 (0.94–1.03)		44%	1.14 (1.04–1.24)	
Hospital volume[e]			.029			.091
Q1	67%	0.96 (0.92–1.00)		37%	1.02 (0.93–1.12)	
Q2	69%	0.99 (0.95–1.04)		37%	1.09 (0.99–1.19)	
Q3	67%	0.94 (0.90–0.98)		35%	0.97 (0.88–1.07)	
Q4	68%	Ref		34%	Ref	

Abbreviations: Q, quintile; ref, referent; RR, relative risk; SES, socioeconomic status.
[a]SES, region, and hospital volume were missing for 101 of 8,005 of cases (1%). These patients have been removed from the analysis.
[b]Modified Poisson regression was used to estimate the RRs.
[c]Log-binomial regression was used to estimate the RRs.
[d]SES is reported by quintile. Q1 represents the lowest SES group.
[e]Q4 represents highest hospital volume.

study period (deaths from 2006–2010) the use rate was 26%. Advanced age, increased comorbidity, lower SES, and female sex were associated with a reduced likelihood of receiving systemic palliative chemotherapy. Large regional differences in treatment rates exist that were not explained by regional differences in case mix. The likelihood of seeing a medical oncologist was lower for patients with advanced age, of female sex, with higher comorbidity, of lower SES, and from certain geographic regions. Finally, consistent with the evolution of clinical trial evidence, use of Gem/platinum chemotherapy increased over time, most notably from the late 1990s to early 2000s, and the use of Gem/Carbo increased somewhat later.

Table 4. Chemotherapy Regimens Used in the Last 12 Months of Life by Study Period

Chemotherapy regimen	Year of Death 1995–1999 (n=215)	2000–2004 (n=283)	2005–2009 (n=479)	*P* Value[a]
Gem/Cis	≤5 (<5%)	84 (30%)	191 (40%)	<.001
Gem/Carbo	≤5 (<5%)	32 (11%)	117 (24%)	<.001
MVAC	45 (21%)	22 (8%)	11 (2%)	<.001
Gem	26 (12%)	50 (18%)	56 (12%)	.253
Other	141 (66%)	95 (34%)	104 (22%)	<.001

Abbreviations: Carbo, carboplatin; Cis, cisplatin; Gen, gemcitabine; MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin.
[a]Cochran-Armitage test for trend.

Although comparison trials to placebo or best supportive care studies for advanced bladder cancer have not been performed, MVAC was compared with cisplatin alone or cisplatin combinations in 2 pivotal trials,[4,21] and showed superior overall survival, establishing multiagent chemotherapy as an option in patients with advanced bladder cancer. A subsequent study comparing MVAC with the combination of Gem/Cis showed similarity in efficacy outcomes with the newer regimen with a median survival of 14 months, but with less toxicity in the Gem/Cis arm, which resulted in its adoption as a standard treatment option.[22]

The use of carboplatin in patients unwilling or unsuitable for cisplatin therapy has been based on lower-level evidence, with no trials comparing single-agent gemcitabine with Gem/Carbo or best supportive care. A phase II/III trial published in 2012 comparing Gem/Carbo versus methotrexate, carboplatin, and vinblastine showed superiority of Gem/Carbo in terms of safety in patients unfit for cisplatin.[23]

Based on these studies, guidelines for the use of palliative chemotherapy in patients with bladder cancer generally recommend Gem/Cis or ddMVAC[6] as first-line chemotherapy options based on the evidence from randomized controlled trials. For patients unsuitable for these types of chemotherapy, carboplatin or taxane-based doublets or single agents are recommended, based on lower-level evidence.

In order for guideline-recommended therapy to be used, several steps need to be taken. Chemotherapy must be considered, offered, discussed, accepted, and received. A total of 68% of our patients saw a medical oncologist, with some regional variation. Even among those patients who met with a medical oncologist, chemotherapy was only delivered in 36%. Whether the low use for patients who saw a medical oncologist is the result of chemotherapy not being considered, discussed, or offered by the physician, or due to an informed patient not determining chemotherapy to be acceptable is unclear and not assessable from a database. Clearly, a substantial portion of the low use of chemotherapy in this cohort relates to the advanced age and high rates of comorbidity, both of which may affect the likelihood that chemotherapy will be offered or accepted.

Patients with advanced bladder cancer have comparable prognosis, comorbidities, and treatment options to patients with advanced pancreatic cancer and advanced non–small cell lung cancer. In advanced pancreatic cancer, Oberstein et al[24] examined SEER data from the United States, and showed that the likelihood of receiving single-agent gemcitabine was 57% in the 1,012 patients older than 65 years with stage IV disease diagnosed in 2004–2005. This population was similar to the bladder cancer population in our study in terms of the advanced age and high comorbidity scores. It is notable that 34% of patients older than 80 years received chemotherapy for advanced pancreatic cancer, compared with 8% of patients older than 80 years receiving chemotherapy for bladder cancer in our study.

Ritzwoller et al[25] showed in a US health maintenance organization setting that 55% of patients received some form of systemic therapy within 4 months of diagnosis of stage III or IV non–small cell lung cancer. Rasco et al[26] also showed in a single-institution setting that 50% of patients received chemotherapy. In contrast, among a population of patients in Manitoba, Canada, with advanced lung cancer older than 70 years, Baunemann et al[27] showed that only 30% saw a medical oncologist,

21% were offered chemotherapy, and 16% accepted and received chemotherapy.

In both lung and pancreatic cancer, predictors of chemotherapy use are largely the same as those shown here: SES, region of treatment, comorbidity score, and age.

Although bladder cancer is not increasing in age-adjusted incidence, it is a disease of the aged and the absolute numbers will continue to increase as the population ages.[28] It should be noted that the median age of patients in the relevant clinical trials was 63 to 65 years,[2,22] whereas 70% of our patients were older than 70 years at the time of death.

Our results highlight the discrepancy between guideline-recommended therapy and practice in routine care of patients with advanced bladder cancer. Not surprisingly, they also highlight the different characteristics between the clinical trials population and the real-world population in terms of age, comorbidity, and SES. To our knowledge, this is the first population-based report in bladder cancer to evaluate this issue. Similar phenomena have been described in the management of patients with potentially curable muscle-invasive bladder cancer.[11]

Two opportunities exist at the population level to improve outcomes for patients with bladder cancer. The first opportunity is to optimize the use of chemotherapy in the patients for whom it was intended. If the reasons for low chemotherapy use are system-related factors, such as variable access to medical oncology consultation, then addressing these systems may improve outcomes. If the reasons are patient- or physician-related beliefs around the risks and benefits of platinum-based chemotherapy for a perceived relatively modest survival advantage, then understanding these beliefs will help improve care or direct research.

The second opportunity would be to recognize that, for a number of reasons, it is likely that conventional chemotherapy is either not feasible, not acceptable, or not deliverable to most patients dying of bladder cancer. Even if chemotherapy use were optimized and standardized, there would still be a large proportion of patients unsuitable or unwilling to take chemotherapy. The development of new nonchemotherapy agents with different toxicity profiles may provide more acceptable treatment options to patients. The testing of these agents specifically in elderly patients and those with comorbidities may increase the adoption of therapy in the general population.

There are several limitations to this study. Because the receipt of palliative chemotherapy was defined as any chemotherapy received in the last 12 months of life, patients would not have been included had they received chemotherapy and lived for more than 12 months after their last dose of chemotherapy. This percentage is, however, fairly small, because only an additional 3% of patients received their last chemotherapy between 12 months and 5 years before death.

One of the difficulties in registry data, as was evidenced in the SEER database review, is that many patients with bladder cancer are initially entered into a database with stage I cancer, but this group comprises more than 50% of the patients who ultimately receive intravenous chemotherapy.[12] For these patients, the time of interest regarding whether they are eligible for chemotherapy is when they develop advanced disease. This date cannot be assessed accurately from our databases, which is why a "look-back" from the date of death was used. Clinical factors, such as performance status and weight loss, which may be strong predictors of chemotherapy use, could not be assessed from our database either at the time of diagnosis or at the time of chemotherapy decisions.

A third concern regards the accuracy of our definition of "death from bladder cancer." Being both an aged population and one with a very high frequency of other malignancies, the risk of misclassification exists. If all patients with multiple malignancies were excluded, results may have been significantly biased, given that 22% of patients had multiple malignancies, and excluding those with multiple malignancies would have excluded a disproportionate number of older patients. Registry data also have the possibility of misclassification bias. For bladder cancer, given the advanced age and comorbidity status of these patients, this may be particularly relevant. Previous work has validated cause of death as being reasonably accurate in the OCR.[29,30] In addition, although death from bladder cancer may be accurate, not all of these patients would have died from metastatic disease, with a portion dying of local progression and from complications of therapy.

Conclusions

In summary, we found low use rates for palliative chemotherapy among patients with advanced bladder cancer, indicating a gap between evidence and practice. Further work is needed to better understand this observed gap and to identify barriers and enablers to delivering evidence-based care to patients with bladder cancer in an effort to improve patient outcomes in real-world practice outside of clinical trials. It is also evident that, although a gap exists between evidence and practice, one also exists between practice and evidence, with most patients dying of bladder cancer bearing little resemblance to those on clinical trials of palliative chemotherapy.

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