

Oncologists' and Primary Care Physicians' Awareness of Late and Long-Term Effects of Chemotherapy: Implications for Care of the Growing Population of Survivors

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Abstract

Purpose: The population of cancer survivors is large and growing. Yet after successful completion of treatment, many experience chemotherapy-related late or long-term effects (LEs). The extent to which physicians are aware of LEs is unknown.

Methods: We conducted a nationally representative survey of 1,130 oncologists and 1,072 primary care providers (PCPs). Respondents were asked to select the LEs they had either observed or seen reported for five chemotherapy agents used to treat breast and colon cancers. We described and compared oncologists' and PCPs' awareness of the specified LEs. Using multivariate logistic regression models, we determined predictors of physicians' awareness of the main LEs associated with the agents.

Results: Almost all oncologists (95%) reported awareness of cardiac dysfunction as an LE of doxorubicin and peripheral neurop-

athy as an LE of paclitaxel (97%) and oxaliplatin (97%). These LEs were reported by 55%, 27%, and 22% of PCPs, respectively. Most oncologists reported awareness of premature menopause (71%) and secondary malignancies (62%) as LEs of cyclophosphamide, compared with only 15% and 17% of PCPs, respectively. Main LEs associated with all four agents were identified by 65% of oncologists and only 6% of PCPs.

Conclusion: Although more than half of PCPs were aware of cardiac dysfunction as an LE of doxorubicin, awareness of other LEs was limited. Because PCPs may not be directly exposed to chemotherapy-related LEs, oncologists must communicate this information to PCPs as patients transition to primary care settings. Education for all providers caring for the growing population of cancer survivors is needed.

Introduction

There are more than 13 million cancer survivors in the United States, and this population is expected to grow to 18 million by 2022.¹ Although cancer treatment has been effective in increasing survival, many survivors experience chemotherapy-related late or long-term physical effects (LEs).¹⁻¹¹ Late effects arise months to years after cancer treatment is over, whereas long-term effects arise during treatment and persist after treatment has ended. There is existing evidence about treatment-related LEs among survivors of pediatric cancers² and expanding information about LEs among survivors diagnosed as adults. Commonly reported chemotherapy-associated LEs in this population include cardiomyopathy, peripheral neuropathy, and premature menopause^{1-8,10,11} as well as secondary cancers.^{3-7,9}

With the growing population of survivors, particularly the elderly and those with comorbidities,¹ and the anticipated shortages in the oncology workforce,^{12,13} focus has been placed on the transition of survivors to primary care settings. Data show that survivors are often observed in nononcology settings¹⁴⁻¹⁷ and that primary care providers (PCPs) are willing to care for this population of patients.¹⁸ However, they may not be confident in the knowledge and skills needed to care for cancer survivors.¹⁹ Oncologists¹⁹ and survivors^{18,20-22} have also expressed concerns about the role of PCPs in survivorship care,

particularly with respect to recognition and management of LEs. To our knowledge, prior studies have not evaluated or compared PCPs' and oncologists' awareness of LEs among adult cancer survivors. Using the Survey of Physician Attitudes Regarding the Care of Cancer Survivors (SPARCCS),¹⁹ a large, nationally representative survey, we described and compared PCPs' and oncologists' awareness of chemotherapy-associated LEs. We also compared and tested associations between awareness of the main LEs associated with chemotherapy agents and selected physician characteristics.

Methods

Study Population and Data Collection

The sample design, recruitment strategy, instrument development, and pilot testing of SPARCCS have been previously described.¹⁹ Briefly, the survey was fielded in 2009 and focused on physician beliefs, knowledge, attitudes, and practices regarding breast and colon cancer survivorship care. These cancers were selected because they are most common among survivors diagnosed as adults, are often encountered by oncologists and PCPs, are generally associated with long survivorship periods, and have existing guidelines for follow-up care.^{23,24} Separate surveys were sent to PCPs and oncologists, with similar items tailored to respective specialties.

The American Medical Association Masterfile was used to identify 5,275 nationally representative PCPs (family practice, internal medicine, or obstetrics/gynecology) and medical oncologists (oncology and/or hematology). Screener telephone calls were placed to the physicians' offices to verify eligibility and confirm contact information. To be eligible, physicians had to practice in a nonfederal practice setting, be age < 76 years, and spend $\geq 20\%$ of their time devoted to patient care. Medical oncologists had to have cared for patients with breast or colon cancer in the past year, and PCPs had to practice in an office-based setting. The full survey instrument is available on request from the National Cancer Institute.²⁵

Of the 5,275 physicians in the initial sample, 1,679 were excluded at the time of the screener telephone calls (details previously described¹⁹). Surveys were sent to the remaining 3,596 physicians. A total of 1,072 PCPs and 1,130 oncologists responded. The weighted survey response rate excluding non-locatable physicians (cooperation rate) was 65.1%; the absolute response rate, including unscreened physicians with unknown eligibility, was 57.6% (PCPs, 57.9%; oncologists, 58.3%).²⁶ Sampling and nonresponse weights were calculated using replicate jackknife methods to ensure that the survey population reflected all practicing US PCPs and oncologists. The study was approved by the National Cancer Institute Institutional Review Board and US Office of Management and Budget.

Outcome

The outcome for this analysis was PCPs' and oncologists' awareness of LEs of chemotherapy, either by direct observation or by exposure to clinical information. Specifically, we asked respondents the following: "Cancer treatment often has adverse effects that may result in morbidity or premature mortality. These adverse effects of cancer treatment can be classified as late or long term . . . Which of the following adverse effects have you observed (or seen reported) most often with use of the following cancer drugs?" Item response included a table listing five chemotherapy agents used to treat breast and/or colon cancers (doxorubicin, cyclophosphamide, paclitaxel, fluorouracil, and oxaliplatin). The brand names of the first three agents were provided in the survey to facilitate recognition. The table also listed five LEs, including cardiac dysfunction, premature menopause, secondary malignancies, pulmonary fibrosis, and peripheral neuropathy. Physicians were asked to select the LE they had either observed or seen reported for each of the chemotherapy agents.

Covariates

Physician characteristics included age (classified as < 40, 40 to 49, 50 to 59, and ≥ 60), sex, race, and ethnicity (white, Asian/Pacific Islander, Hispanic, African American, other), US or foreign trained, American Board of Medical Specialties board certified, and specialty (medical oncology, hematology/oncology, other oncology, general internal medicine, family medicine, obstetrics/gynecology). Practice characteristics included main practice location (physician owned, large group/health maintenance organization, hospital/clinic), time spent on patient care

($\leq 50\%$, 51% to 90%, $> 90\%$), and number of patients with breast or colon cancer seen per year for PCPs (≤ 20 , 21 to 30, > 30) and per week for oncologists (≤ 25 , 26 to 35, > 35). Finally, we assessed physicians' self-reported confidence in their knowledge of the physical late effects of breast and colon cancer treatment, categorized as not at all confident, somewhat confident, or very confident.

Statistical Analyses

SAS-callable SUDAAN (release 10.0.1; Research Triangle Institute, Research Triangle Park, NC) was used for weighted survey data. Rao-Scott χ^2 tests were used to examine bivariate relationships between covariates of interest and physician type and to compare oncologists' and PCPs' responses for each individual chemotherapy agent/LE pair. All statistical tests were two sided and performed at the .05 level of significance.

First, we assessed the percentages of physicians who reported observing the LEs or seeing the LEs reported. Second, for four of the chemotherapy agents, we selected the main associated LEs. Specifically, we defined cardiac dysfunction as the LE most often associated with doxorubicin,^{4,11,27-30} premature menopause or secondary malignancies with cyclophosphamide,^{5,6,8,9,31-33} and peripheral neuropathy with both paclitaxel and oxaliplatin.^{7,10,34,35} We excluded fluorouracil because LEs for this agent have not been commonly reported. Third, using weighted multivariate logistic regression modeling, we examined the relationship between oncologists' identification of all four mainly associated LEs for the specified chemotherapy drugs and a number of a priori physician (age, sex, race/ethnicity, and training) and practice (percentage of patients uninsured, location type, time spent on patient care, and number of patients with breast and/or colon cancer per year) covariates. In the modeling analysis, we chose premature menopause (over secondary malignancies) as the more commonly associated LE for cyclophosphamide. In a separate model, we added the effect of physicians' confidence in their knowledge as a covariate to the previously described model. The results of the two models were similar; therefore, we only report the latter. Because of the low numbers of PCPs identifying all of the main LEs, we did not conduct regression modeling for this outcome but rather assessed predictors of PCPs' awareness of cardiac dysfunction as a main LE associated with doxorubicin.

Results

Study Population

Characteristics of the 1,072 PCPs and 1,130 oncologists are listed in Table 1. There were no statistically significant differences among respondents and nonrespondents.¹⁹ Age distribution was mixed, and most physicians were men, white, US trained, and board certified. Among the PCPs, approximately 40% were family practitioners, 40% were internists, and 20% were obstetricians/gynecologists. Most oncologists reported being very confident in their knowledge of physical LEs of breast (77%) and colorectal cancers (76%) compared with 23% and 31% of PCPs, respectively.

Table 1. PCP and Oncologist Characteristics

Characteristic	PCPs (n = 1,072; %)*	Oncologists (n = 1,130; %)*
Age, years		
< 40	22	30
40-49	33	29
50-59	31	25
≥ 60	14	16
Sex		
Female	35	27
Male	65	73
Race/ethnicity		
White	70	63
Asian	15	28
Hispanic	7	4
Black or African American	5	2
Other	3	3
US trained		
Yes	76	64
No	24	36
Board certified		
Yes	82	90
No	18	10
Specialty		
Medical oncology	N/A	48
Hematology/oncology	N/A	52
General internal medicine	37	N/A
Family medicine	43	N/A
Obstetrics/gynecology	20	N/A
Percentage of patients uninsured		
≤ 5	62	67
6-25	29	21
26-100	5	4
Main practice location		
Physician-owned practice	66	56
Large medical group/HMO	17	11
Hospital	16	30
Percentage of time spent on patient care		
≤ 50	5	10
51-90	44	58
> 90	51	32
No. of patients with breast or colon cancer per year†		
≤ 20	45	N/A
21-30	15	N/A
> 30	33	N/A
No. of patients with breast or colon cancer per week‡		
≤ 25	N/A	44
26-35	N/A	19
> 35	N/A	37

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Table 1. (Continued)

Characteristic	PCPs (n = 1,072; %)*	Oncologists (n = 1,130; %)*
Self-reported confidence in knowledge of physical late effects		
Breast cancer		
Not at all	15	1
Somewhat	61	22
Very	23	77
Colon cancer		
Not at all	14	1
Somewhat	54	22
Very	31	76

NOTE. Frequencies may not always add to 100% because of missing values.

Abbreviations: HMO, health maintenance organization; N/A, not applicable; PCP, primary care provider; SD, standard deviation.

* All percentages were weighted using jackknife replicate weighting methods.

† Mean of 37 patients (SD, 1.4) per year reported by PCPs.

‡ Mean of 35 patients (SD, 0.8) per year reported by oncologists.

Awareness of LEs

Awareness of LEs most commonly associated with the specified chemotherapy agents by direct observation or as reported varied (Table 2). For doxorubicin, 55% of PCPs and 95% of oncologists responded as having observed or seen reported cardiac dysfunction as an associated LE. For cyclophosphamide, 15% of PCPs and 71% of oncologists identified premature menopause as an LE, and 17% and 62% identified secondary malignancies, respectively. Peripheral neuropathy was identified as an associated LE for paclitaxel by 27% of PCPs and 97% of oncologists and, for oxaliplatin, by 22% of PCPs and 97% of oncologists. Additional LEs that the PCPs and oncologists responded as having observed and/or reported are listed in Table 2.

Predictors of LE Awareness

Appendix Figure A1 (online only) shows the percentages of physicians who responded as having observed and/or reported the main LEs associated with the four chemotherapy agents (doxorubicin, cyclophosphamide, paclitaxel, and oxaliplatin). Overall, only 60 PCPs (6%) reported awareness of all four associated LEs, compared with 744 oncologists (65%). In adjusted analyses (Table 3), we found that among oncologists, awareness was associated with being oncology board certified (odds ratio [OR], 1.68; 95% CI, 1.07 to 2.65) and spending most of their time on patient care (51% to 90% of time: OR, 1.90; 95% CI, 1.24 to 2.91; > 90% of time: OR, 1.82; 95% CI, 1.08 to 3.07). Those reporting less confidence in their knowledge of LEs of breast cancer treatment were less likely to report awareness of LEs (OR, 0.61; 95% CI, 0.39 to 0.94); this association was not observed for self-reported knowledge of colon cancer treatment. Age, sex, race, and other characteristics were not associated with LE awareness.

PCPs' awareness of cardiac dysfunction as an LE associated with doxorubicin was less likely among family medicine physi-

Table 2. PCPs (n = 981) and Oncologists (n = 1,125) Reporting Awareness of LEs for Each Chemotherapy Agent*

LE	Doxorubicin			Cyclophosphamide			Paclitaxel			Oxaliplatin			Fluorouracil		
	PCPs (%)	Oncologists (%)	P	PCPs (%)	Oncologists (%)	P	PCPs (%)	Oncologists (%)	P	PCPs (%)	Oncologists (%)	P	PCPs (%)	Oncologists (%)	P
Peripheral neuropathy	8	1	< .001	17	3	< .001	27	97	< .001	22	97	< .001	13	8	< .001
Pulmonary fibrosis	8	1	< .001	13	21	< .001	6	5	NS	9	5	< .001	2	2	NS
Cardiac dysfunction	55	95	< .001	7	8	NS	6	5	NS	1	0	NS	7	22	< .001
Premature menopause	7	67	< .001	15	71	< .001	13	31	< .001	2	15	< .001	3	15	< .001
Secondary malignancies	5	48	< .001	17	62	< .001	3	4	NS	2	4	.008	6	4	.03
Do not know	36	0.5	< .001	51	6	< .001	56	1	< .001	71	2	< .001	66	27	< .001

NOTE. For doxorubicin, main LE is cardiac dysfunction; for paclitaxel and oxaliplatin, main LE is peripheral neuropathy; for cyclophosphamide, main LEs are premature menopause and secondary malignancies (indicated by bold font).

Abbreviations: LE, late or long-term effect; PCP, primary care provider.

* Total of 96 respondents (4%) skipped section (PCPs, n = 91; oncologists, n = 5).

cians and obstetricians/gynecologists (OR, 0.26; 95% CI, 0.19 to 0.37 and OR, 0.27; 95% CI, 0.15 to 0.48, respectively) than among general medicine physicians (data not shown). Awareness was positively associated with the number of patients with breast or colon cancer seen per year (26 to 30 patients: OR, 1.68; 95% CI, 1.07 to 2.64; ≥ 36 patients: OR, 1.59; 95% CI, 1.14 to 2.22) compared with ≤ 25 patients.

Discussion

In a nationally representative study, we found that although more than half of PCPs had either observed or seen reported cardiac dysfunction as an LE of doxorubicin, awareness of other LEs was limited (< 30%). Most oncologists (> 95%) were aware of the main LEs for doxorubicin, paclitaxel, and oxaliplatin. Although fewer were aware of the main LEs for cyclophosphamide (62% to 71%), awareness of these LEs was significantly higher among oncologists than PCPs. Because PCPs may not be directly exposed to chemotherapy and its LEs in practice or literature, oncologists must clearly communicate information about these potential LEs as patients transition to primary care settings. Furthermore, education for all providers caring for cancer survivors is needed.

Prior literature has shown that chemotherapy has toxic LEs. Early recognition of these effects may result in improved long-term function and reduced debilitating symptoms. For other effects, such as cardiomyopathy, timely diagnosis and management may also reduce mortality.^{36,37} Whereas some LEs may occur when patients are still receiving care in oncology settings, others may not present until years after treatment, when patients and/or their PCPs may not be focused on cancer. As such, without awareness of LEs, symptoms may either be discounted (eg, young adult with shortness of breath who had been treated with doxorubicin) and/or attributed to other causes (eg, patient with neurologic symptoms undergoing advanced imaging to identify etiology), thus leading to misinformed evaluation and possibly delayed and/or inappropriate treatment. It is important that PCPs and oncologists are aware of potential LEs, diagnose them in a timely manner, and offer management options when possible.

The limited reported awareness of LEs by PCPs is not surprising. PCPs may not directly encounter chemotherapy agents and/or their LEs in clinical practice and may not be attuned to the medical literature reporting associations between the agents and LEs. Medical education and training have not traditionally promoted awareness of LEs and/or survivorship issues by focusing on the acute treatment of patients with cancer. Only recently have programs begun to include specific instruction about survivorship.³⁸⁻⁴⁰ Even with expanding curricula, it may be unreasonable to expect PCPs to be aware of all potential LEs, particularly given the diversity of cancers and the ever-expanding list of available treatment options, including biologics. Therefore, mastery of LEs will likely remain within the purview of oncology providers and thus may provide impetus for shared care of long-term survivors. However, our study also highlights the gaps in oncologists' awareness of LEs, particularly cyclophosphamide. There is a need to integrate cancer survivorship education and training for all providers caring for patients with cancer. Training and current practice must emphasize communication between oncologists and PCPs about the long-term care needs of cancer survivors.

To facilitate communication and coordination as a patient transitions from an oncology to primary care setting, the Institute of Medicine has recommended that a cancer survivorship care plan (SCP) be developed at the completion of treatment and shared with the PCP and patient.⁴¹ The SCP should include details about treatment, possible LEs, and surveillance recommendations, among others. However, despite these recommendations, provision of SCPs in practice has been limited; data have suggested that their completion is fraught with challenges for busy oncology practices.^{42,43} Although descriptive studies have suggested that SCPs may be beneficial to PCPs and their patients,^{18,20,44-48} a recent randomized controlled trial of SCPs conducted in the breast cancer population showed no benefit on the measured outcomes.⁴⁹ To our knowledge, the effect of SCPs on communicating information about LEs to PCPs has not been evaluated.

Our study has some important strengths. It involved a large, nationally representative survey with a good response rate. To

Table 3. Multivariable Adjusted Predictors of Oncologists' Awareness of Main LEs of All Chemotherapy Agents (n = 1,123)*

Predictor	OR	95% CI
Age, years		
< 40	1.00	Referent
40-49	1.13	0.78 to 1.64
50-59	1.09	0.73 to 1.62
≥ 60	0.73	0.47 to 1.14
Sex		
Male	1.00	Referent
Female	1.14	0.78 to 1.70
Race/ethnicity		
White	1.00	Referent
Asian/Pacific Islander	1.67	0.46 to 0.99
Hispanic	1.37	0.68 to 2.77
African American	0.58	0.24 to 1.37
Other	0.86	0.36 to 2.05
US trained		
Yes	1.00	Referent
No	0.85	0.61 to 1.20
Board certified		
No	1.00	Referent
Yes	1.68	1.07 to 2.65
Specialty		
Medical oncology	1.00	Referent
Hematology/oncology	1.17	0.88 to 1.56
Other oncology	0.86	0.23 to 3.20
Location		
Physician-owned practice	1.00	Referent
Large medical group/HMO	0.93	0.59 to 1.45
Hospital	0.97	0.69 to 1.35
Other	0.84	0.29 to 2.45
Percentage of uninsured patients		
< 5	1.00	Referent
5-25	0.78	0.59 to 1.03
> 26	0.59	0.31 to 1.15
Percentage of time spent on patient care		
< 50	1.00	Referent
51-90	1.90	1.24 to 2.91
> 90	1.82	1.08 to 3.07
No. of patients with breast or colon cancer per week		
≤ 25	1.00	Referent
26-35	1.38	0.96 to 1.98
≥ 36	1.12	0.85 to 1.49
Self-reported confidence in knowledge of physical		
Colon cancer		
Very confident	1.00	Referent
Not/somewhat confident	1.08	0.71 to 1.65

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Table 3. (Continued)

Predictor	OR	95% CI
Breast cancer		
Very confident	1.00	Referent
Not/somewhat confident	0.61	0.39 to 1.94

NOTE. For doxorubicin, main LE is cardiac dysfunction; for paclitaxel and oxaliplatin, main LE is peripheral neuropathy; for cyclophosphamide, main LE used in model is premature menopause. Bold font indicates $P < .05$.

Abbreviations: LE, late or long-term effect; OR, odds ratio; PCP, primary care provider.

* No. is slightly smaller than 1,130 because of missing information for variables of interest.

our knowledge, it was the first to document awareness of LEs among PCPs and oncologists based on direct observation or literature. We did not rely on recall, because the items asked physicians to select LEs for each of the chemotherapy agents (rather than to provide answers to open-ended question). Our study focused on survivors of breast or colon cancer, commonly encountered by PCPs in general medical practice, thus giving them an opportunity to have observed the LEs in question or to have read about them in the literature. Although the number of breast and/or colon cancer survivors reported being seen annually by the PCPs may have been relatively low compared with the most commonly reported chronic medical conditions,⁵⁰ the prevalence of cancer in the population is significant (ranging from 8% among those age 60 years to 64% to 19% among those age 80 to 84 years).⁴¹ With the aging population, cancer prevalence in primary care settings will continue to increase.

Our study does have limitations. First, we specifically assessed awareness of LEs by asking physicians to report direct exposure and/or medical literature and did not specifically test knowledge. Thus, if physicians responded that they had seen a particular LE in practice or in the literature, we could not assess if their answer was correct. For example, LEs have not been commonly reported for fluorouracil. It may be that they mistakenly attributed a late effect to a chemotherapy agent, but it is also possible they had indeed observed this LE in their practices. On the contrary, failure to identify cardiac dysfunction for doxorubicin, premature menopause or secondary malignancies for cyclophosphamide, or peripheral neuropathy for paclitaxel or oxaliplatin (all commonly reported LEs), was considered incorrect and indicated lack of awareness. Unlike oncologists, PCPs have limited opportunities to observe LEs in practice or see reports of LEs. Interestingly, > 50% of PCPs reported awareness of cardiac dysfunction as being associated with doxorubicin. It is possible that PCPs have more frequent exposure to patients with breast cancer in their practices, that cardiac dysfunction is more prevalent, and/or that doxorubicin-related cardiac dysfunction may be more commonly reported in general medical literature. Because of sample size limitations, we were not able to assess independent predictors of PCPs' characteristics associated with awareness of all main LEs, but we did evaluate predictors of PCPs' awareness of cardiac dysfunction as an LE of doxorubicin. The differences we found by specialty may be targeted for future educational interventions. Finally,

because our study focused on chemotherapy agents used to treat two common cancers, it is likely that awareness of less commonly used agents not analyzed here would be lower among both PCPs and oncologists.

In summary, we found PCPs' awareness of LEs by either observation or literature was limited for most agents. Because PCPs do not typically encounter chemotherapy agents and/or their LEs in their clinical practices and may not be exposed to relevant literature, the latter finding is not surprising. However, it warrants attention. In the transition of patients from oncology to primary care settings, PCPs should be informed about potential LEs so that they are better prepared to recognize and address them among the cancer survivors in their care. Furthermore, there is a need for ongoing education among all physicians who care for cancer survivors about LEs of cancer treatment.

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Appendix

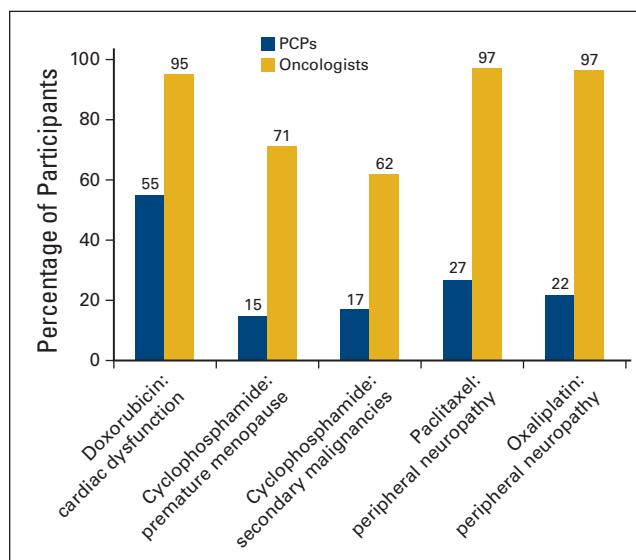


Figure A1. Percentage of participants who responded as having observed and/or reported main late or long-term effects associated with four chemotherapy agents. PCP, primary care provider.