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Patient/Provider Discussions About Clinical Trial Participation and Reasons for Nonparticipation Among Adolescent and Young Adult Women with Cancer

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Purpose: Clinical trial enrollment is low among adolescents and young adults (AYAs) with cancer and may contribute to inferior survival gains in recent years in this population compared with other age groups. We investigated clinical trial participation among AYA women with cancer, and examined whether patients discussed clinical trial participation with their doctor and reasons for nonparticipation.
Methods: Women with a diagnosis of breast cancer, thyroid cancer, melanoma, lymphoma, or gynecologic cancer at ages 15–39 years during 2004–2016 were identified from the North Carolina Central Cancer Registry and the Kaiser Permanente Southern California health system. During 2018–2019, a total of 1264 eligible women completed an online survey (response = 13%), which examined survivorship issues among AYAs.
Results: Overall, 5% of participants reported that they had participated in a clinical trial. Most women reported that they had not discussed clinical trial participation with a medical provider (76%) and that they did not know whether a relevant trial was available for their cancer (73%). Among those who knew that a trial was available but did not participate, the most commonly reported reasons for nonparticipation included concerns about side effects of the treatment in the trial and concerns that the treatment had not been sufficiently tested. ***Conclusion:*** Only a small proportion of AYA women with cancer in our cohort reported discussing a clinical trial with a provider or knowing whether a relevant trial was available. Our findings point to opportunities to improve patient/provider communication to increase clinical trial enrollment among AYAs with cancer.

Keywords: clinical trials, breast cancer, lymphoma, thyroid cancer, melanoma, gynecologic cancer

Introduction

Adolescents and young adults (AYAs, ages 15–39) account for more than 70,000 new cancer diagnoses each year in the United States, approximately seven times the number of new cases among children under age 15 years.[1,2] Although 5-year relative survival among AYAs with cancer has increased steadily since the 1970s, improvements have lagged significantly behind those experienced by either children or older adult cancer patients.[3] This finding, documented in multiple reports over the past decade,[4–7] has contributed to a burgeoning of the field of AYA oncology and widespread interest in efforts to improve outcomes for AYA patients.

Although a multitude of factors likely play a role, one commonly suggested reason for the inferior survival gains among AYAs with cancer is low participation among AYAs in clinical trials.[2,8] While between 40% and 60% of cancer patients under age 15 reportedly enroll in a clinical trial, similar estimates for AYAs with cancer are typically <20%,[9] with some estimates as low as 6%.[10,11] The reasons for nonparticipation in trials among AYA patients remain poorly understood, although limited availability of relevant trials, lack of patient or physician knowledge of available trials, problems accessing available trials, and patient concerns about participation in research have been cited as among the potential reasons in prior studies.[9,11,12] However, studies of clinical trial participation to date have tended to focus on

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AYAs with leukemias, lymphomas, germ cell tumors, and sarcomas.[11,13,14] AYA patients with other cancer types, including some of the most common among AYAs, such as breast cancer, have seldom been examined.[10,15] Additionally, while several AYA studies have described associations between patient demographic and treatment characteristics and likelihood of enrollment in a clinical trial, few have investigated provider/patient communication about trial participation or patient knowledge of trial availability. A discussion of trial availability and patient eligibility is a necessary early step upon which many of the subsequent steps in enrollment are predicated. In the current study, we investigated clinical trial participation among AYA women with breast cancer, thyroid cancer, melanoma, gynecologic cancers, and lymphomas, and examined whether patients discussed clinical trial participation with their doctor and reasons for nonparticipation in this population.

Methods

Study population

We used data from the Horizon study, a study established to investigate reproductive outcomes among AYA women with cancer. AYA women with an incident cancer diagnosis were identified using data from the North Carolina Central Cancer Registry and the Kaiser Permanente Southern California (KPSC) health system. Eligible women were diagnosed with breast cancer, thyroid cancer, melanoma, lymphoma (Hodgkin lymphoma [HL] or non-Hodgkin lymphoma [NHL]), or gynecologic cancer (ovarian cancer, cervical cancer, or uterine cancer) at ages 15–39 years during 2004–2016 and were alive as of December 31, 2016 for North Carolina cases or December 26, 2018 for KPSC cases. Cancer types were defined according to the AYA Site Recode ICD-O-3/WHO 2008 definition.[16] During 2018–2019, a total of 12,398 eligible women were mailed a letter, which invited them to participate in an online survey and provided a link to the survey and login information. Of these, 2494 letters were returned as undeliverable (20%). Of the 9904 letters that were not returned, 1296 women participated in the survey (13%). Among the 1296 participants, 1264 had full information available for this analysis.

Clinical trial measures

Questions pertaining to clinical trial enrollment were adapted from those used in the AYA Health Outcomes and Patient Experience (AYA HOPE) Study.[11,17] The introduction to the clinical trials section of the online survey stated: ''Clinical trials are research studies that may include surgery, radiation, chemotherapy, drugs, or other treatments. Clinical trials are sometimes also called experimental studies or protocols.'' All participants were then asked whether they discussed the possibility of a clinical trial or experimental study with a medical provider and whether there were clinical trials or experimental studies available for their type or stage of cancer. Possible response options for these questions were ''Yes,'' ''No,'' and ''I am not sure.'' Those who responded that there were clinical trials or experimental studies available were asked whether they participated in one. Those who indicated that they had discussed the possibility with a medical provider and that there were trials available were also asked whether a doctor recommended that they participate in a trial. Participants who reported that there were trials available for their type or stage of cancer but that they did not participate in one were presented with a list of 11 possible reasons for nonparticipation and asked to indicate whether or not each was a reason for them (i.e., multiple reasons could be selected).

Other measures

Cancer information, including cancer type, age at diagnosis, and year of diagnosis, were ascertained from the North Carolina cancer registry and the KPSC cancer registry. In the online survey, women provided information on race/ethnicity, education, health insurance status, and school/employment status. Women were also asked to report the location where they received the majority of their cancer care, including the name of the hospital/clinic, the city, and the state. For women who reported that they received the majority of their care in North Carolina, we categorized their hospital type as an National Cancer Institute (NCI)-designated cancer center (Duke, University of North Carolina, and Wake Forest), other academic hospital (housing a medical school), or a nonacademic hospital. We also categorized hospitals according to whether or not they have a residency program, using information from the American Medical Association.[18]

Statistical analysis

Generalized linear regression models were used to estimate prevalence ratios (PRs) and 95% confidence intervals (CIs) for associations between participant characteristics and (1) whether women discussed trials with a medical provider and (2) whether they had knowledge of trial availability. We considered women to have knowledge of trial availability if they responded either ''Yes'' or ''No'' to the question of whether there were clinical trials or experimental studies available for their type or stage of cancer. Those who responded ''I am not sure'' to this question were considered not to have knowledge of trial availability. Multivariable models were adjusted for cancer type and age at diagnosis.

Results

A total of 1264 women were included in these analyses. The most common cancer types among participants were breast cancer (41%) and thyroid cancer (23%), and most women were diagnosed at ages 30–39 years (74%) (Table 1). The majority of women were non-Hispanic White (74%) and had health insurance at diagnosis (96%).

Overall, 67 participants (5%) reported that they had participated in a clinical trial. Across cancer types, participation ranged from 0% among women with gynecologic cancers to 11% among women with breast cancer. Most women (76%) reported that they had not discussed the possibility of participating in clinical trial with a medical provider (Table 2). The majority of women overall indicated that they were not sure whether a trial was available for their type or stage of cancer (73%), whereas only 11% reported knowing that a relevant trial was available. The proportion unsure whether a trial was available ranged from 64% among women with breast cancer to 84% among women with thyroid cancer.

Table 1. Descriptive Characteristics of 1264 Women with an Adolescent And Young Adult Cancer Diagnosis in North Carolina or Kaiser Permanente Southern California During 2004–2016

Cancer type		
Breast	515	41%
Lymphoma	131	10%
Gynecologic[a]	144	11%
Thyroid	297	23%
Melanoma	177	14%
Site		
North Carolina	929	73%
KPSC	335	27%
Age at diagnosis		
15–19	29	2%
20–24	102	8%
25–29	194	15%
30–34	346	27%
35–39	593	47%
Mean (SD)	32.6	(5.5)
Race/ethnicity		
Non-Hispanic White	931	74%
Non-Hispanic Black	82	6%
Hispanic	164	13%
Other	86	7%
Missing	1	
Education at survey		
High school or less	77	6%
Some college	410	32%
Bachelor's degree	448	35%
Graduate degree	328	26%
Missing	1	
Calendar year of diagnosis		
2004–2009	427	34%
2010–2016	837	66%
Student at diagnosis (full time or part time)		
No	1075	85%
Yes	189	15%
Insurance at diagnosis		
Uninsured	47	4%
Any Medicaid	69	5%
Other insurance	1147	91%
Missing	1	
Hospital type[b]		
NCI cancer center	225	25%
Academic, not NCI	118	13%
Nonacademic	544	61%
Missing	8	
Residency program[b]		
No	424	48%
Yes	463	52%
Missing	8	

[a]Includes cervical, uterine, and ovarian.
[b]Among those who received the majority of their cancer care in of North Carolina.
KPSC, Kaiser Permanente Southern California; NCI, National Cancer Institute; SD, standard deviation.

Knowing that a relevant trial was available was most common among women with breast cancer (21%). In total, 170 women (13%) indicated that they had not discussed trials with a provider but had knowledge of whether or not a trial was available. Among those who discussed trials with a provider and knew that a relevant trial was available for their type or stage of cancer ($N = 113$), a total of 92 (81%) indicated that their doctor had recommended participation. Of these 92 participants, 65 (71%) reported having participated in a trial.

In multivariable models, women with melanoma, gynecologic cancers, lymphoma, and thyroid cancer were significantly less likely to have discussed clinical trials with a provider than women with breast cancer (Table 3). Women with these cancer types were also less likely than women with breast cancer to know whether a trial was available. Discussion of clinical trials did not differ substantially according to age. However, older AYAs (age 30–39) were less likely to indicate knowledge of trial availability than younger AYAs (age 15–29; PR = 0.78; 95% CI: 0.63–0.97). Compared with women treated in nonacademic settings, those treated in an NCI-designated cancer were more likely to have discussed clinical trials (PR = 1.47; 95% CI: 1.09–1.99) and to know whether a relevant trial was available (PR = 1.51; 95% CI: 1.20–1.90). Treatment in a hospital/clinic with a residency program was also associated with knowledge of trial availability (PR = 1.30; 95% CI: 1.05–1.61). Women of race/ethnicities other than non-Hispanic White appeared less likely to have discussed clinical trials with a provider (PR = 0.76; 95% CI: 0.58–1.01), although estimates were imprecise; race/ethnicity was not strongly associated with knowledge of trial availability.

Among 77 women who knew that a relevant clinical trial was available but did not participate, the most commonly reported reasons for nonparticipation included worry about the side effects of the treatment in the trial (30%) and worry that the treatment had not been sufficiently tested (27%) (Table 4). These were followed by thinking that the trial would not be helpful (19%) and worry that she would get a placebo or sugar pill rather than the actual treatment (19%). In total, 16% reported that family or work responsibilities prevented participation.

Discussion

In this study of 1264 women with an AYA cancer diagnosis, the majority of participants reported not having discussed the possibility of clinical trial participation with a medical provider and not knowing whether a relevant trial was available for their type or stage of cancer. Participation in a trial was reported by 5% of women overall and, across cancer types, ranged from 0% among women with gynecologic cancers to 11% among women with breast cancer. Among women who knew that a relevant trial was available but did not participate, the most common reasons for nonparticipation were related to concerns about the treatment being given in the trial. These findings highlight gaps in communication between patients and providers as a potential contributor to low rates of clinical trial participation among AYAs with cancer.

Although estimates of clinical trial enrollment among AYAs with cancer have been consistently low, ranging from 6% to 18% across prior reports,[10,13–15] the likelihood of participating in a trial has been shown to vary according to characteristics such as cancer type, age at diagnosis, and treatment setting.[12] Adolescents (ages 15–19) are generally more likely to enroll in a clinical trial than older AYAs,[12] particularly if they are treated in a pediatric setting.[10,15] For older AYAs, who are more often treated in community-based oncology settings, there may be fewer opportunities to enroll

Table 2. Responses to Clinical Trials Questions Among 1264 Women with an Adolescent And Young Adult Cancer Diagnosis in North Carolina or Kaiser Permanente Southern California During 2004–2016

	All participants, N (%)	*Breast cancer,* n *(%)*	*Lymphoma,* n *(%)*	*Gynecologic cancer,* n *(%)*	*Thyroid cancer,* n *(%)*	*Melanoma,* n *(%)*
When you were diagnosed with cancer, did you discuss the possibility of a clinical trial or experimental study with a medical provider?						
Yes	210 (17)	157 (30)	24 (18)	12 (8)	8 (3)	9 (5)
No	965 (76)	305 (59)	96 (73)	122 (85)	277 (93)	165 (93)
I am not sure	89 (7)	53 (10)	11 (8)	10 (7)	12 (4)	3 (2)
When you were diagnosed with cancer, were there clinical trials of experimental studies available for your type or stage of cancer?						
Yes	144 (11)	109 (21)	12 (9)	7 (5)	7 (2)	9 (5)
No	201 (16)	77 (15)	25 (19)	28 (19)	42 (14)	29 (16)
I am not sure	919 (73)	329 (64)	94 (72)	109 (76)	248 (84)	139 (79)
When you were diagnosed with cancer, did a doctor recommend that you participate in a clinical trial?[a]						
Yes	92 (81)	76 (84)	8 (89)	1 (25)	4 (100)	3 (50)
No	20 (18)	13 (14)	1 (11)	3 (75)	0 (0)	3 (50)
I am not sure	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
When you were diagnosed with cancer, did you participate in a clinical trial or are you still a part of a clinical trial regarding your cancer diagnosis?[b]						
Yes	65 (71)	57 (75)	4 (50)	0 (0)	2 (50)	2 (67)
No	27 (29)	19 (25)	4 (50)	1 (100)	2 (50)	1 (33)

[a]Among those who discussed it and knew a relevant trial was available.
[b]Among those who discussed it, knew a relevant trial was available and a doctor recommended participation.

Table 3. Characteristics Associated with Discussing Clinical Trials with a Provider and Knowledge of Trial Availability Among 1264 Women with an Adolescent And Young Adult Cancer Diagnosis in North Carolina or Kaiser Permanente Southern California During 2004–2016

	Discussed trial with provider		*Knowledge of trial availability*	
	Unadjusted OR (95% CI)	*Multivariable-adjusted OR (95% CI)*[a]	*Unadjusted OR (95% CI)*	*Multivariable-adjusted OR (95% CI)*[a]
Cancer type[b]				
Breast	1	1	1	1
Lymphoma	0.60 (0.41–0.88)	0.56 (0.37–0.85)	0.78 (0.58–1.05)	0.70 (0.51–0.95)
Melanoma	0.17 (0.09–0.32)	0.16 (0.08–0.31)	0.59 (0.44–0.81)	0.55 (0.40–0.75)
Gynecologic	0.27 (0.16–0.48)	0.27 (0.15–0.47)	0.67 (0.49–0.92)	0.65 (0.48–0.89)
Thyroid	0.09 (0.04–0.18)	0.08 (0.04–0.17)	0.46 (0.35–0.60)	0.42 (0.32–0.56)
Age at diagnosis[c]				
15–29	1	1	1	1
30–39	1.52 (1.10–2.10)	0.86 (0.62–1.20)	1.00 (0.81–1.22)	0.78 (0.63–0.97)
Per year	1.05 (1.02–1.07)	1.00 (0.97–1.02)	1.01 (0.99–1.03)	0.99 (0.97–1.01)
Race/ethnicity				
Non-Hispanic White	1	1	1	1
Other	0.83 (0.62–1.12)	0.76 (0.58–1.01)	1.14 (0.94–1.39)	1.11 (0.91–1.35)
Hospital type[d]				
NCI cancer center	1.21 (0.87–1.68)	1.47 (1.09–1.99)	1.40 (1.11–1.77)	1.51 (1.20–1.90)
Academic, not NCI	1.26 (0.84–1.89)	1.16 (0.79–1.70)	1.18 (0.86–1.62)	1.13 (0.83–1.55)
Nonacademic	1	1	1	1
Residency program[d]				
No	1	1	1	1
Yes	1.15 (0.87–1.54)	1.18 (0.90–1.54)	1.30 (1.04–1.61)	1.30 (1.05–1.61)

[a]Adjusted for cancer type and age at diagnosis.
[b]Adjusted estimates are adjusted for age at diagnosis only.
[c]Adjusted estimates are adjusted for cancer type only.
[d]Among those who received majority of their cancer care in North Carolina.
CI, confidence interval; OR, odds ratio.

Table 4. Reasons for Nonparticipation Among Women Who Knew a Relevant Trial Was Available but Did Not Participate ($N=77$)

	N	%
I was worried about side effects of the treatment in the clinical trial	23	30
I was worried that I might receive a treatment that had not been sufficiently tested	21	27
I did not think that a clinical trial would help me	15	19
I was worried that I might get a placebo or sugar pill rather than actual treatment	15	19
I had family (i.e., parenting) or work responsibilities that prevented participation	12	16
I was worried that I might be treated like a guinea pig	9	12
My insurance would not cover part or all of the payment for the clinical trial	8	10
I was worried that I would have to switch doctors to participate in a clinical trial	8	10
I could not find a clinical trial available in a medical facility near me	8	10
I could not find a clinical trial that was available for my cancer type or stage	7	9
I was too sick to have a treatment in a clinical trial	5	6

Participants could select more than one reason. Therefore *N*s do not sum to total and percentages do not sum to 100%.

in trials. Using medical record data for AYA patients with NHL, HL, acute lymphocytic leukemia (ALL), and sarcoma in the 2012–2013 NCI Patterns of Care Studies, Parsons et al. reported that while 44% of patients 15–19 years of age enrolled in a clinical trial, only 5% and 6% did so among patients 30–34 and 35–39 years of age, respectively.[14] In their study, enrollment in a trial was more common among AYAs with ALL (42%) and sarcoma (31%) than those with HL (9%) or NHL (7%); receiving treatment in a hospital with a residency program was also associated with trial enrollment. Others have also documented a greater likelihood of enrollment among AYAs with leukemia and sarcoma than among those with other cancer types, such as lymphomas, breast cancer, and gynecologic cancers.[15]

Most of the clinical trial questions in our study were adapted from those used in the AYA HOPE Study, a cohort of 515 AYAs diagnosed with ALL, germ cell tumor, lymphoma, or sarcoma and identified from Surveillance, Epidemiology, and End Results program (SEER) registries.[11] Interestingly, despite differences in the cancer types included, the proportion of women in our study who reported participation in a clinical trial (5%) is similar to that reported in AYA HOPE (6%). Given that most cancer types in our study tend to occur primarily in older AYAs (i.e., breast cancer and gynecologic cancers), or are generally associated with excellent prognosis (i.e., thyroid cancer and melanoma), we expected that an even smaller proportion of women in our study would report trial participation. Women with breast cancer made up a large proportion of our sample and were most likely to report having participated in a trial and knowing that a relevant trial was available, suggesting that breast cancer trials are likely greater in number or more accessible than trials for other cancer types we examined.

Among AYA HOPE participants, only 17% reported knowing that a relevant trial was available for their type and stage of cancer, whereas 63% did not know whether a relevant trial was available.[11] Not knowing whether a relevant trial was available was even more common in our cohort, reported by nearly 73% overall and ranging from 64% to 84% across cancer types. For lymphomas, included in both our cohort and AYA HOPE, the proportion of patients not knowing about trial availability was only slightly higher in our study (72%) than in theirs (HL: 62.4%, NHL: 62.5%).

In our cohort, the high proportion lacking knowledge of relevant trial availability reflects the low proportion (17% overall) that recalled discussing the possibility of trial participation with a medical provider, an issue which was not examined in the AYA HOPE Study. For cancer types in our cohort associated with excellent prognosis, such as melanoma and thyroid cancer, physicians may see little need to investigate available trials or discuss them with patients, since patients would be unlikely to derive additional benefit from participation in a trial, even if one were available. Reporting a discussion about clinical trials with a provider was most common among women with breast cancer and lymphoma, cancers which are often more aggressive and more difficult to manage than others we examined. However, even for these cancer types, fewer than one-third of participants recalled discussing the possibility of trial participation, indicating an opportunity for improved communication between physicians and patients to increase clinical trial enrollment among AYAs. This may be particularly true for AYAs treated in community oncology settings, where trials may be less available or providers may have limited knowledge about available trials; receiving care in a nonacademic setting was associated with a lower likelihood of discussing clinical trials with a provider in our analyses. Interestingly, 13% of women in our study indicated that they knew whether or not a relevant trial was available, despite reporting that they had not discussed trials with a provider. This suggests that some AYA patients may be doing their own research to find open trials relevant for their cancer.

Although a relatively small proportion of women in our study had discussed trials with a medical provider and knew that a relevant trial was available, it is encouraging that nearly three-quarters of these women participated in a trial if doing so was recommended by their doctor. We did not have a sufficient sample size to evaluate characteristics associated with participation among those for whom a doctor recommended it. However, our results indicate that AYAs with cancer may often be amenable to enrolling in a clinical trial if encouraged to do so by a physician.

Irrespective of discussion about clinical trials with a medical provider or physician recommendation to participate, several reasons for nonparticipation were reported by women in our sample who knew that a relevant clinical trial was available but did not participate. The most commonly endorsed reasons were concerns about possible side effects or insufficient testing of the treatment in the trial. These were also the two most frequent reasons for nonparticipation among AYA HOPE participants, reported by 32% and 39%, respectively.[11] Similar concerns have been frequently reported among cancer patients of other age groups as well,[8] highlighting a potential need for strategies to mitigate these concerns. In our cohort, 16% of women reported that family (i.e., parenting) or work responsibilities prevented participation, a reason which was not evaluated in AYA HOPE. This highlights the fact that there are AYA-specific barriers to enrollment as well that should be considered by providers.

Discussing these barriers with patients, and identifying existing resources to address them, may increase the likelihood of trial enrollment among some AYAs.

This study is among the first AYA-specific studies to examine clinical trial participation among patients with cancer types, such as breast cancer, thyroid cancer, melanoma, and gynecologic cancers. It is also one of the first to investigate whether AYAs with cancer discussed clinical trial participation with a medical provider and reasons for nonparticipation among those who knew that a relevant trial was available. Our study also has several limitations. The participation rate for the survey was quite low (12%). However, with >1000 respondents, ours is one of the largest studies to date involving direct contact with AYA cancer survivors. Additionally, information on trial participation was based solely on participant self-report and was not verified through medical records. It is possible that some women may have mistaken participation in another type of research study as participation in a clinical trial. Given that some women were diagnosed several years before completing the online survey, it is also possible that some were unable to accurately recall whether they participated in a trial or discussed participation with a provider. Information from women who died before the survey was initiated was also not captured, and more severe disease may be associated with a greater likelihood of discussing and participating in a trial. Finally, women in our study were predominantly non-Hispanic White and insured, and findings may not be generalizable to more diverse patient populations.

Few AYA women with cancer in our cohort reported discussing a clinical trial with a provider or knowing whether a relevant trial was available for their cancer type or stage. Many also had concerns about participating in a trial that could be addressed during discussions with providers. Our findings point to opportunities to improve patient/provider communication to increase clinical trial enrollment among AYAs with cancer.

Author Disclosure Statement

No competing financial interests exist.

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