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Why Do Few Cancer Patients Enrol into Clinical Trials?

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Abstract

Nationwide, only 3% of cancer patients participate in clinical trials. While many barriers to clinical trial enrollment have been identified in the literature, we sought to identify the prevalent reasons for non-participation over a six-month period after initial visit at our institution in four cancer sites: non-small cell lung cancer, pancreas, prostate and breast.

In addition to improving trial enrollment numbers, there is a need to ensure that cancer patients and their disease [1] have a fit with a trial at the treating institution (Patient-Trial Fit), [2] are given the opportunity to participate and, [3] accept enrollment [15,18]. Patient-trial fit can be divided into three steps: there being a trial available for the patient's condition, the patient's meeting the study's eligibility criteria, and the treating physician's judgment that the benefits outweigh the risks for this patient. Opportunity includes discussion of trials and the specific trial's risks and benefits with the patient and then the patient having interest in the particular trial. Acceptance of a trial includes patient consent to participate and study enrollment. These steps make up our framework for inclusion of patients in clinical trials [18]. At each of these steps or points of decision, there are reasons for failing to proceed with participation.

We set out to determine, at one comprehensive cancer center, the reasons cancer patients fail to enroll onto therapeutic clinical trials. We detail the number of patients not enrolled and reasons at each step for non-participation. In this study we report the most prevalent reasons for non-participation by cancer site.

Records from 688 medical oncology new (diagnosis in 2010-13) patient charts were reviewed and abstractions conducted to assess reasons cited for nonparticipation in cancer clinical trials during their initial six-month treatment period.

This analysis underscores institutional barriers to enrollment that have the potential to direct solutions to trial enrollment at our institution.

Introduction

There are known obstacles in clinical trials such as drug preparation, approvals, and testing and limits on spending from any disease sector [1,2]. While patient education and navigation may increase enrollment by reducing participant burden [3] decreasing barriers of knowledge [4] and improving access to trials [5,6], the impact of these interventions on clinical trial participation has been limited. Nationwide, only 3% of cancer patients participate in clinical trials [7,8] Understanding the lack of participation in cancer clinical trials is needed to improve this statistic.

Shorter distance [9] or travel time to a cancer center [10] treatment at a cancer center [11], an appealing treatment [12], lifestyle factors, use of the internet [13], patient preferences [14], and other factors [15] impact the probability that a patient will participate in a trial. Even though the proportion of patients who participate in clinical trials at cancer centers is higher [16] the

majority of patients do not participate in any therapeutic study. Institutional efforts must be informed by systematic and thorough examination of enrollment [17] and an accounting of the reasons patients do not enroll in clinical trials made.

In addition to improving trial enrollment numbers, there is a need to ensure that cancer patients and their disease [1] have a fit with a trial at the treating institution (Patient-Trial Fit), [2] are given the opportunity to participate and, [3] accept enrollment [15,18]. Patient-trial fit can be divided into three steps: there being a trial available for the patient's condition, the patient's meeting the study's eligibility criteria, and the treating physician's judgment that the benefits outweigh the risks for this patient. Opportunity includes discussion of trials and the specific trial's risks and benefits with the patient and then the patient having interest in the particular trial. Acceptance of a trial includes patient consent to participate and study enrollment. These steps make up our framework for inclusion of patients in clinical trials [18]. At each of these steps or points of decision for patients, there are reasons for failing to proceed with participation.

We set out to determine, at one comprehensive cancer center, the reasons new cancer patients fail to enroll onto therapeutic clinical trials. The framework [18] was used to detail the number of patients not enrolled and reasons at each step for non-participation. In this study we report the most prevalent reasons for non-participation.

Methods

Medical oncology records from a consecutive series of new breast (N=293), non-small cell lung (NSCLC, N=154), pancreas (N=146) and prostate (N=94) cancer patients were abstracted. Charts for new patients were abstracted from the day of first visit at the cancer center to 6 months later. One hundred percent of patients seen in a pre-specified time period were abstracted. Abstractions were conducted of new patient charts visiting our cancer center during January-March 2013 for NSCLC; December 2012-March 2013 for breast cancer; June 2010- March 2013 for pancreas; January-April 2010 for prostate cancer.

Demographic factors of age (continuous; and <59, 60-69, and ≥70), sex (male or female), race (white, black or other) were also abstracted. Additional factors abstracted from individual records informed the three sequential steps of patient-trial-fit, opportunity, and acceptance [18].

The reason for not enrolling in a clinical trial was also retrieved from the medical record. Reasons were initially abstracted verbatim from the chart. Each observation was recoded into logical categories of "No Available Trials for Eligible Patients", "Standard Treatment Recommended or Current Treatment Preferred", "Distance to The Cancer Center", "Care Received Elsewhere or Patient Didn't Return" or "Other".

Chi square statistics were used to assess demographic differences; patient-trial-fit, opportunity, and acceptance among cancer sites; and the prevalent reasons patients did not enroll in a clinical trial.

This study was approved by the Johns Hopkins School of Medicine Institutional Review Board.

Results

Only the demographic factors of race and age differed among cancer sites in these newly diagnosed patients. The percentage of black patients was highest in NSCLC (25%) and lowest in pancreas (8%). The largest preponderance of cancer patients under age 60 was found in breast (60%) and the smallest in prostate (17%). The sex distribution did not differ between NSCLC and pancreas cancer (p=0.920). (Table 1)

	Breast (N=293)	NSCLC (N=154)	Pancreas (N=146)	Prostate (N=94)	p Value
Race					
White	202 (69%)	110 (71%)	127 (87%)	78 (83%)	0.0012
Black	52 (18%)	27 (25%)	11 (8%)	11 (12%)	
Other	39 (13%)	17 (11%)	8 (5%)	5 (5%)	
Sex					
Males	6 (2%)	76 (49%)	74 (51%)	94 (100%)	0.920*
Females	287 (98%)	78 (51%)	72 (49%)	0 (0%)	
Age					
≤59	175 (60%)	56 (36%)	56 (38%)	16 (17%)	<0.0001
60-69	69 (24%)	57 (37%)	61 (42%)	37 (39%)	
≥70	49 (17%)	41 (27%)	29 (20%)	41 (44%)	
*Contrasting NSCLC and pancreas only. P values are based on chi square tests.					

Table 1: Patient demographics by cancer site, JH SKCCC.

The four most prevalent reasons for non-enrollment were: no available trials for eligible patients (36-55%); standard treatment was recommended or current treatment was preferred (6-23%); lost to clinical follow-up or patient chose to receive care elsewhere (5-14%); and distance from the cancer center (1-22%). Combined, these 4 reasons eliminate 64% of breast, 83% of pancreas, 84% of prostate and 89% of NSCLC patients from trial participation. (Table 2).

	Number	No Available Trials for Eligible Patients	Standard Treatment Recommended or Current Treatment Preferred	Care Received Elsewhere or Patient Didn't Return	Distance from the Cancer Center	Four Reasons Combined
		p=0.005*	p<0.001	p=0.071	p<0001	p<0001
Breast	293	106 (36%)	39 (13%)	29 (10%)	13 (4%)	187 (64%)
NSCLC	154	78 (51%)	36 (23%)	21 (14%)	2 (1%)	137 (89%)
Pancreas	146	81 (55%)	9 (6%)	8 (5%)	24 (16%)	122 (84%)
Prostate	94	43 (46%)	9 (10%)	6 (6%)	21 (22%)	79 (84%)

Table 2: Most prevalent reasons for no enrollment by cancer site, JH SKCCC.

Of the patients remaining after accounting for these four reasons, 47% (50/106) of breast, 47% (8/17) of NSCLC, 71% (17/24) of pancreas, and 73% (11/15) of prostate patients enrolled.

Enrollment into a therapeutic clinical trial was highest in breast at 17% (50/293), next in pancreas (17/146) and in prostate (11/94) at 12%, and lowest in NSCLC at 5% (8/154).

Discussion

The study results suggest that the four most common reasons account for the majority of non-participation and that addressing each of these reasons may increase clinical trial participation percentages. In order, they are [1] no available trials for eligible patients, [2] standard treatment recommended or preferred, [3] care obtained elsewhere or didn't return to care or [4] distance from the cancer center. Each set of reasons represents an opportunity to increase participation at cancer centers.

Though no available trials for eligible patients is the most common reason cancer patients at our institution, irrespective of cancer site (Table 2) the second most prevalent reason reveals two patterns. Among pancreas and prostate cancer patients, distance is identified as the reason for not participating in clinical trials, while amongst breast and NSCLC patient's standard treatment or current treatment was second. Prostate and pancreas patients are also more often white (Table 1), unreflective of Baltimore city demographics. These patients are traveling greater distances, as measured by cancer-site-specific catchment area as well [19].

No Available Trials for Eligible Patients

Not having a trial available for potentially eligible patients is by far the most common reason for fall off. Dropping out of consideration for a clinical trial is at least three times as likely because of gaps in the clinical trial portfolio and restrictive eligibility criteria compared to any of the other three reasons. Solutions are complex and multifaceted. Anwuri and colleagues opened new trials with availability in mind for the patients who attend their clinics. This along with other institutional changes increased participation in trials at their institution. [16]. Regarding narrow eligibility criteria, legitimacy of the criteria revolves around scientific inference, patient safety, and unambiguously defined constraints on participation [20]. Eligibility criteria for every study should be critically reviewed to also ensure generalizability of the trial results. Solutions must deal with both availability and eligibility in a way that promotes a cohort of trial participants who are more representative of the patients treated here.

Standard Treatment is Recommended or Preferred

This study also examined the first six months of cancer care at our cancer center for new patients, irrespective of diagnosis date or prior treatment. Some patients have begun a standard therapy, which physician and patient agree should be continued, while other patients prefer the standard treatment because the chances of benefiting from a trial are no more than 50% [21]. This reason for not participating in a trial should perhaps be addressed with patients through awareness and information strategies. In the meantime, researchers' discussion of the potential but unknown merits of a new treatment may not be enough either since trials as a whole discover 25-50% of successful treatments [22]. Moreover, optimal clinical trial design involves enriching the study population with those who are thought most likely to benefit. [23] Interestingly, Cheng and colleagues found trouble recruiting may be detected with the simple indicator of delayed start-up of more than 2 months [24]. This measure may be used with investigators to review trial particulars. As an example of one way to address the desire for standard care, standard care is being combined with additional

therapeutics for NSCLC based on biomarkers.

Care Was Obtained Elsewhere or The Patient Didn't Return to Care

Continuity of care establishes levels of interaction, solidifies a doctor-patient relationship and addresses the element of trust in the treatment establishment [25,26]. Nevertheless, a regional cancer center may be used to obtain second opinions about standard and experimental treatment. As many as a third of these patients are looking for a different diagnosis [27], which when not confirmed sends the patient back to their "Home Provider" to resume consultation. Timing of the patient visit relative to current treatment is critical in determining whether there is a trial available when the consulting patient is first seen at the cancer center [28]. For various reasons, community physicians often do not participate in clinical trials due to the need of adequate infrastructure to support clinical research [29].

Distance to The Cancer Center

Distance to the source for treatment is a frequently mentioned barrier to clinical trial participation [12,30] and particularly true of minority populations [9]. Even in the case when a catchment area is small, if geography makes access to care difficult, it will also influence enrollment in clinical trials. Longer travel time [31] and ease of travel [32] are equated with distance by patients. Patient unwillingness or inability to travel has been addressed mainly by engaging community physicians in a network as clinical trial providers. This strategy addresses only a portion of the pool of potential clinical trials since not all trials are amenable to distributed enrollment. Distance may be one of a number of reasons patients do not receive their care at a cancer center [33] and perhaps there is a solution in acknowledging a shared responsibility by health systems and trial supporters. In response to this finding, we have designed a study of whether enhanced access to transportation increases clinical trial participation.

This study has some limitations such as being a retrospective look at enrollment processes through chart review. Tracking enrollment for patients for only six months may have biased the results to less participation since as their disease progresses, additional trials are open to patients. Time periods for data collection were somewhat staggered but were during periods when there were no particular efforts to improve clinical trial participation. Though it was the same abstraction form in use, there were four reviewers who abstracted charts, which may have made a difference in the results between programs. Each abstractor however used the framework as a guide in data collection, abstracted the same information for each patient, and captured the reasons verbatim (later categorized).

Discussion

This is one study, at one cancer center, which focuses on just four cancer sites. Nevertheless, it is revealing that enrollment is high among those who have not reported one of the four reasons: "no available trials for eligible patients", "standard treatment is recommended or preferred", "care was obtained elsewhere or the patient didn't return", and "distance to the cancer center" (range: 47% of breast to 73% of prostate cancer patients). This situation can be addressed through trial designs that meet the needs and circumstances of the patients who seek cancer treatment at SKCCC.

Conclusion

This analysis underscores barriers to enrollment that have the potential to direct solutions to low enrollment at our institution. We plan to assess which barriers can be most effectively addressed in order to initiate and evaluate some remedies, understanding that approaches will differ across disease types and the patient demographics.

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