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ORIGINAL PAPER

Evaluating the decisions of glioma patients regarding clinical trial participation: a retrospective single provider review

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Abstract

Clinical trial accrual is vital to advancing care. A single study elucidated demographic data correlating with glioma patients' clinical trial enrollment. However, it did not investigate the underlying decision-making process for non-participation. In this study, we seek to understand this key aspect of patient accrual. All notes for glioma patients seen by a single neuro-oncologist from July 2010 to May 2017 were examined for mention of clinical trial offerings. When a trial was declined, the patient's reasoning was recorded along with the following: diagnosis, KPS, extent of resection, age, gender, race, marital status, income group, religion, trial offered at initial visit versus subsequent, and distance from trial site. Of 279 consecutive glioma patients, 88 were eligible for and offered a clinical trial. Fifty-seven accepted (65%), and 31 (35%) declined participation (Fig. 1). Of those offered a clinical trial, patients with glioblastoma (GBM) were significantly more likely to accept (44 out of 57 (77%) vs. 13 out of 57 (23%), $p=0.03$). After we adjusted for gender and travel distance, GBM was the only significant predictor of clinical trial acceptance, with an odds ratio of 3.18 (95% CI 1.17, 8.61, $p=0.02$). Reasons cited for non-participation included: travel distance (39%), lack of interest (39%), visit frequency (16%), and fear of randomization (6%). This study clarified for the first time individual glioma patient rationale for non-participation and potential areas for improving enrollment. Allowing off-site treatment centers or telemedicine visits may entice rural patients to participate. Visit frequency should be carefully considered and minimized whenever possible. Further prospective study of rationale for non-participation may improve enrollment over time.

Keywords Glioma · Clinical trial · Accrual · Evaluating decisions · Non-participation

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Introduction

Medical oncology relies heavily on clinical trials to determine the most effective therapy. Behind each chemotherapy approved by the FDA, there are multiple clinical trials and often hundreds of patients who agree to try the novel therapy. Unfortunately, accrual of patients for oncology clinical research trials has become increasingly difficult leading to approximately one out of three cancer clinical trials to close early due to failure to enroll [1–3]. Without enough patients, clinical trial investigators may decrease their treatment group sizes to meet their accrual targets, thus decreasing the power of these studies and preventing detection of subtle differences [4].

Poor accrual can be attributed to three major categories: trial design/eligibility criteria, physician awareness and attitude, and patient demographics and beliefs. Of recent, strict eligibility requirements have been questioned, especially considering the many new precision medicine studies

focusing on highly specific genomic targets and the need to be maximally inclusive [5, 6]. The role providers play in this dynamic has also been investigated. These physician-related barriers include: poor communication with patients (lack of compassion/respect, tone of voice, being rushed, etc…), physicians being uncomfortable discussing clinical trials, physicians not offering trials due to comorbidity concerns despite meeting eligibility criteria, and negative physician attitude towards trials due to the burden of data collection and associated costs [7–9].

As for patient-related factors, they can be broken into two parts: demographics and beliefs/reasoning behind their decisions. One of the seminal papers regarding disparities in cancer clinical trials found that patients greater than 65 years (across a range of 15 tumor types) were significantly underrepresented, including glioma patients. Only 19% of glioma patients in clinical trials were > 65 years old despite the fact that 44% of glioma patients are older than 65 [10]. Other demographic barriers such as race, rural location, and low socioeconomic status have been identified [11–13]. A systematic review was conducted by Ford et al. to discern the barriers to enrollment of underrepresented populations and the top five reasons for declining trial were: mistrust of research, perceived harms, associated costs, transportation, and patient demographics [14].

While demographic correlates for non-participation in glioma trials have been investigated, this study uniquely provides a better understanding of the explicit patient reasoning. It is the only study in glioma patients wherein their stated reasons for declining trial participation were available. All other studies focusing on glioma patients have relied on using database de-identified demographic patient correlates and were not able to access specific patient notes. The largest study analyzing the accrual of glioma patients utilized the Glioma Outcomes (GO) Project database, a prospective observational database that captures clinical practice patterns. Using that data, the investigators correlated medication and demographic data such as age, gender, race, household income, education level, and use of complementary and alternative medicine with the likelihood of clinical trial enrollment. The main findings showed younger patients and Caucasian patients had increased enrollment in clinical trials [13]. While these results help define what populations need to be targeted, racial and ethnic minority groups as well as older patients (> 65), it does not tell us why these groups of people are less inclined to participate in clinical trials.

The missing piece to improving accrual for glioma clinical trials and recruiting a diverse patient population is understanding the patient's rationale for why he/she chooses to not participate in a clinical trial. Each patient has a unique set of beliefs and ideas which factor into his/her decisions. Analyzing how patients respond after being asked to participate in a clinical trial delves deeper into barriers to accrual than demographic data alone. For this reason, we evaluated an individual neuro-oncologist's notes as the physician described in detail the responses from patients who declined to participate in clinical trials to gain a deeper understanding of this key aspect of accrual.

Methods

Patient data

This study was approved by the Institutional Review Board, and a waiver of consent was granted as all patient information was de-identified. Data were collected from each glioma patient's medical record seen by a single neuro-oncologist at an academic medical center from July 2010 to May 2017. Patients under 18 years of age at initial consult and those without decision-making capacity were excluded. Each patient's consult and progress notes were examined to see if a clinical trial was offered. If the patient was offered trial and declined, the patient's reasoning (as documented in the physician's note) was recorded in complete detail and then further classified into four all-inclusive groups: travel distance, not interested, randomization, or visit frequency. These categories were established based off the aggregate subjective reasons for declining trial available from the chart. While slight variations of the explicit reasoning exist, each patient's true thoughts can be explained by these categories. If a patient was offered trial and accepted but later failed screening before beginning the clinical trial, he/she was considered as having accepted the trial. The following demographic data for each patient offered trial was obtained: diagnosis, Karnofsky Performance Status (KPS), extent of resection, age, gender, race, marital status, income group, religion, trial offered at initial visit vs. subsequent, and distance from trial site.

Statistical analysis

Descriptive statistics are described as frequencies (percentages) and medians (ranges) for categorical and continuous variables, respectively. Several factors were evaluated to determine the strength of association with the outcome (participation in a clinical trial) using a Chi square test or Fisher's exact test for categorical data, and a Mann–Whitney test for continuous data. Relevant factors were entered in a multivariable logistic regression model to assess the strength and the direction of association with participation in a clinical trial. All results were considered statistically significant for values of p less than 0.05 significance level. SAS software v9.4 (SAS Institute Inc., Cary, NC) was used for all computations.

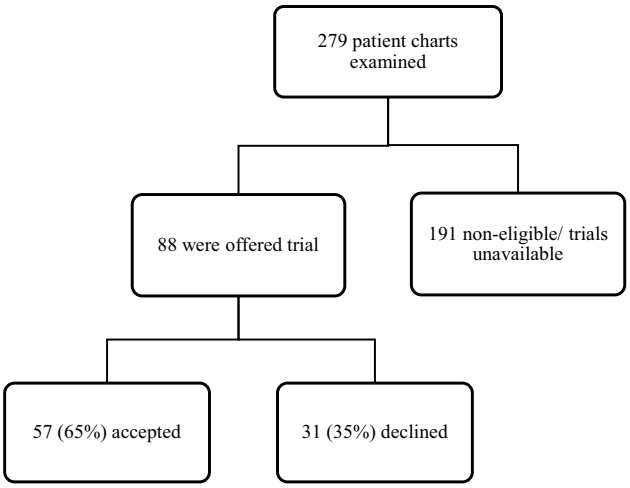

Fig. 1 Flow diagram of patient charts examined

Results

Of 283 consecutive patients for whom charts were manually reviewed, four patients were excluded as they initially accepted a clinical trial but withdrew consent prior to starting. Of the remaining 279 patients, 191 (68%) were not offered a clinical trial as one was not available, or they were ineligible. Of the 88 patients for whom a clinical trial was offered, 57 accepted (65%) and 31 (35%) declined participation (Fig. 1). All patients offered trials that reported English as their primary language and having insurance. Additionally, all respondents confirmed having social support from a family member, a caregiver, or a friend. Therefore, those measures were not included in the characteristic overview. Due to a small sample size, tumor type was dichotomized into glioblastoma (GBM) or non-GBM.

Demographics

Results of demographic and clinical comparisons are presented in Table 1. For the most part, we found no difference in demographic and clinical measures when comparing patients who accepted a clinical trial with those who did not ($p > 0.05$). However, we did find that patients with GBM were more likely to accept trial (44 out of 57 (77%) vs. 13 out of 57 (23%), $p = 0.03$) when compared to patients with any other glioma tumor type. Since our study had more males 34 (56%) than females 27 (44%) diagnosed with GBM, 1.26:1 (M:F), we controlled for tumor type diagnosis in our analysis. We found that gender did not influence glioma clinical trial participation after adjusting for type of tumor ($p = 0.83$) (Table 3). When examining the responses from the 31 patients rejecting a clinical trial, we found that 12 (39%) refused trial participation due to travel distance, 5 (16%) due to visit frequency, 2 (6%) due to treatment randomization, and 12 (39%) showed no interest (Table 2).

Multivariable analysis

The results of the multiple logistic regression analysis are presented in Table 3. After we adjusted for gender and travel distance, GBM was the only significant predictor of clinical trial acceptance. Patients diagnosed with GBM had 3.18 higher odds (95% CI 1.17, 8.61) of enrolling in the trial when compared with non-GBM patients ($p = 0.02$).

Discussion

To understand why glioma patients decline clinical trials, we first analyzed the demographic data to compare our findings with that of other leading studies on barriers to accrual in glioma trials. Although our study's sample size is relatively small ($n = 88$) compared with Chang et al.'s larger study ($n = 708$), demographic and tumor factors still tend to show no statistically significant association with trial participation [13]. Our clinical trial acceptance rate (20.4%), was similar to that of the GO study (21.3%) [13]. Based on our results and those presented from previous studies, it seems that glioma patients have a greater propensity to accept clinical trials compared to most other tumor types, which report clinical trial acceptance ranges from 1 to 10% [11, 12, 15–18]. This finding may be due to the high proportion of GBM patients, who were more likely to choose trial enrollment, consistent with the findings in the GO project [13]. The median overall survival (OS) of GBM is less than 20 months, compared with grade III and grade II gliomas with an OS range of 1.3–14.7 years and 5–> 20 years, respectively [19–22]. This suggests an inverse correlation between prognosis and willingness to participate in clinical trials. Based on the principles of Kahneman and Tversky's prospect theory, which describes how people choose between probabilistic options based on a risk–benefit analysis, this is not surprising as GBM patients have a dismal prognosis and may perceive a more favorable risk to benefit ratio from trial participation [23]. This effect has also been observed in various other end stage cancers [24]. Following this rationale, it may be that in a larger cohort study, willingness to participate may also increase with subsequent prior recurrences. Additionally, our patient population was overwhelmingly Caucasian (93%). This may be a contributing factor to the high participation rate seen in our study since Caucasians were shown to be more likely to enroll in clinical trials than other races according to previous studies of both glioma and non-glioma patients [12, 13]. Our patients had a relatively homogenously good performance status (median KPS 80–90), which did not affect participation as it is typically an inclusion criterion for clinical trial eligibility.

Table 1 Characteristics of glioma patients who accepted clinical trial (CT) compared with those who did not

Characteristics	Patients $n=88$	Accepted CT $n=57$ (65%)	Rejected CT $n=31$ (35%)	p Value
Tumor description n (%)				
GBM	61	44 (77)	17 (28)	0.03
Other	27	13 (23)	14 (52)	
Age at first contact, median [range]	88	57 [47, 63]	52 [41, 64]	0.32
Gender n (%)				
Male	47	31 (54)	16 (34)	0.80
Female	41	26 (46)	15 (37)	
Race/ethnicity n (%)				
White/Caucasian	82	52 (63)	30 (37)	0.42*
Other	6	5 (83)	1 (17)	
Marital status, n (%)				
Married	67	41 (61)	26 (39)	0.21
Single	21	16 (76)	5 (24)	
Religion n (%)				
Religious	60	42 (70)	18 (30)	0.13
No religious preference	28	15 (54)	13 (46)	
Insurance coverage n (%)				
Yes	87	57 (66)	30 (34)	0.35*
No	1	0	1	
Seen at diagnosis, n (%)				
Yes (initial visit)	72	47 (65)	25 (35)	0.83
No (second opinion)	16	10 (62)	6 (38)	
KPS, median [range]	88	90 [80, 90]	80 [70, 90]	0.21
Distance from UNMC-miles, median [range]	88	47 [13, 65]	34 [14, 124]	0.28
Distance from UNMC n (%)				
City of Omaha	19	13 (68)	6 (32)	0.64
Metropolitan area of Omaha	17	10 (59)	7 (41)	
Less than 60 miles	20	15 (75)	5 (25)	
More than 60 miles	32	19 (59)	13 (41)	
Income group n (%)				
Low	42	31 (54)	11 (35)	0.09
High	46	26 (46)	20 (65)	
Progression n (%)				
First contact	55	36 (65)	19 (35)	0.97*
1st PD	21	13 (62)	8 (38)	
2nd PD	10	7 (70)	3 (30)	
3rd PD	2	1 (50)	1 (50)	
Greatest extension of resection n (%)				
Biopsy	28	20 (71)	8 (29)	0.77
GTR (gross total resection)	31	20 (65)	11 (35)	
NTR (near total resection)	13	8 (62)	5 (38)	
STR (subtotal resection)	16	9 (56)	7 (44)	

GBM glioblastoma, *KPS* Karnofsky Performance Status, *UNMC* University of Nebraska Medical Center, *CT* clinical trial, *PD* progression of disease

*Fisher exact p-value

Review of the most recent data from Central Brain Tumor Registry of the United States (CBTRUS) reveals that not only GBM but all gliomas have a male preponderance, with a ratio ranging from 1.2 to 1.36 for the various histologies and tumor grades [25], and our results were within this range with a ratio of 1.27 M:F. Despite the increased prevalence

Table 2 Patient rationale for rejecting clinical trial

Descriptions	Rejected clinical trial $n=31$ (35%)
Reason for rejecting trial *n* (%)	
Travel distance	12 (39%)
Not interested	12 (39%)
Visit frequency	5 (16%)
Randomization	2 (6%)

Table 3 Univariate and multivariable logistic regression analysis for clinical trial acceptance

Variables	Univariate analysis	Multivariable analysis
	OR (95% CI)	AOR (95% CI)
Gender		
Male	1.12 (0.46, 2.69)	1.10 (0.44, 2.76)
Female	1	1
p Value	0.80	0.83
Tumor type		
GBM	2.79 (1.09, 7.13)	3.18 (1.17, 8.61)
Other	1	1
p Value	0.03	0.02
Travel distance		
≤ 60 mi	1.38 (0.34, 5.61)	1.21 (0.28, 5.17)
> 60 mi	0.67 (0.20, 2.23)	0.48 (0.13, 1.75)
Metro area	0.66 (0.19, 2.59)	0.62 (0.15, 2.60)
City of Omaha	1	1
p Value	0.64	0.49

OR odds ratio, *AOR* adjusted odds ratio

of GBM in males, the GO project found that there was no statistically significant difference in clinical trial participation when comparing genders as did our analysis shown in Table 1.

Travel distance to the trial site and lack of interest were the two primary reasons patients declined clinical trial in addition to visit frequency and fear of randomization to the control arm. Due to the scale of the multi-site GO project, this subjective data was not able to be collected for glioma patients. It is difficult to ascertain why certain patients showed a lack of interest in participating as they simply stated that they did not wish to participate and did not expand upon their reasoning. Other studies have found that negative personal and family attitudes about clinical trials and perceived lack of personal benefit can discourage enrollment, and while the former attitude is difficult to measure, the latter is likely represented by our patients who declined due to randomization. The third patient-centric reason for declining trials found in prior non-oncologic studies is inconvenience [26–28]. Of interest, subjective assessments of travel distance prohibited participation even though there was no statistically significant difference in the actual travel distance between those who accepted trial and those who did not. This study was limited in that the availability of transportation and income was not recorded to discern how this may have affected responses. In attempt to adjust for income, we did estimate patient socioeconomic status by stratifying them based on the median household incomes of their zip codes compared to the Nebraska median household income in 2016 [29]. However, this did not show a statistically significant difference. The patients who declined trial due to the frequency of visits may also be affected by factors of transportation and ability to afford lodging or simply wanting to spend more quality time with family and friends away from the hospital.

Finally, we did not gather information regarding attitudes or potential misconceptions about clinical trials in those who declined. As noted earlier, research has shown these to unfavorably detract from participation in trials. Prospective attempts to improve enrollment should include patient and physician education to both dispel misconceptions about trials and to better prepare oncologists to discuss them.

Conclusions

This study clarified for the first time glioma patients' rationale for non-participation in clinical trials. These findings identify key areas of improvement to enhance accrual of glioma patients and highlight that glioma patients, particularly those with GBM, are very likely to desire participation. Allowing off-site treatment centers or telemedicine visits may entice rural patients or those with limited access to transportation and lodging to participate. Additionally, the frequency of visits should be carefully considered and minimized whenever possible to allow patients to spend more time outside the hospital. Further prospective study of individual patient rationale for non-participation may improve our understanding of these barriers and enrollment over time.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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