Exclusion Criteria of Breast Cancer Clinical Trial Protocols: A Descriptive Analysis

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Abstract

Purpose: 3-8% of US adults with cancer are enrolled in a clinical trial due to various barriers to enrollment. The purpose of this study is to evaluate the variability of eligibility criteria, which currently have no standard guidelines.

Methods: This descriptive analysis utilized all therapeutic breast protocols offered at the University of Alabama at Birmingham between 2004-2020. Exclusion criteria were abstracted using OnCore and ClinicalTrials.gov. Laboratory values included liver function tests and hematologic labs. Comorbid conditions included congestive heart failure, cardiovascular disease, central nervous system (CNS) metastases, and prior cancer history. Comorbid conditions were further analyzed by amount of time protocols required participants to be from diagnosis or exacerbation-free.

Results: 102 protocols were eligible. Among liver laboratory values, bilirubin (78%) was included in most protocols ranging from institutional upper limit of normal (ULN) (9%) to 3xULN (2%), with 1.5xULN (56%) being most common. Similar variability was observed in alanine transaminase and aspartate transaminase. Among hematological labs, 82% of protocols defined a lower limit of acceptable absolute neutrophil count ranging from 500μL (1%) to 1,800μL (1%), with 1,500μL (64%) being most common. Of the comorbid conditions, exclusion criteria varied for congestive heart failure (49%), an acute exacerbation of cardiovascular disease (80%), CNS metastases (59%) and a prior cancer (66%). The allowable timeframe varied between protocols for cardiovascular disease and prior cancer.

Conclusion: Substantial heterogeneity was observed across laboratory values and comorbid variables among protocols. Future research should focus on defining standardized eligibility criteria while allowing for deviation based on drug specificity.

Key Points

Question: The purpose of this study was to evaluate breast cancer clinical trial eligibility criteria**.**

Findings: In this descriptive study, substantial heterogeneity was observed among eligibility criteria for breast cancer clinical trials.

Meaning: There is lack of evidence guiding creation of current eligibility criteria, and future research should focus on defining standardized eligibility criteria while allowing for deviation based on drug specificity.

Background

Clinical trials play an important role in advancing cancer treatments by providing additional therapy options that are not yet available for the general patient population [1, 2]. Unfortunately, only about 3–8% of adults with cancer are enrolled in a clinical trial in the United States [3, 4]. The lack of participation has

been attributed to various causes, one being eligibility (inclusion and exclusion) criteria, which determine a patient's suitability to participate safely in a trial while studying the safety and efficacy of new drugs [2, 5]. Strict eligibility criteria often have the effect of excluding patients older than 65 due to comorbid health conditions [6, 7]. In recent years, ASCO and Friends of Cancer Research have worked to modernize eligibility criteria to allow for a more representative trial population [2, 8, 9] Their work has advocated for including patients that have mild organ dysfunction as exhibited by abnormal laboratory values. However, many protocols also include arbitrary exclusionary parameters (e.g. no significant cardiovascular disease in the past 6 months) for comorbid conditions that can make it difficult for clinicians to properly apply clinical trial outcomes to patient populations [10]. The purpose of this study is to evaluate the variability of eligibility criteria among breast cancer clinical trials.

Methods

Study design and sample

This descriptive study used all breast cancer-specific therapeutic clinical trials open at the University of Alabama at Birmingham (UAB) from 2004–2020 (Table 1). After eligible studies were identified, inclusion and exclusion criteria were obtained from study protocols housed in OnCore and from ClinicalTrials.gov. This study was approved by UAB's Institutional Review Board (IRB).

Table 1
Protocol cancer characteristics (N = 102)

	Frequency (%) **N = 102**
Cancer Stage	
Early	34 (33.3)
Late	58 (56.9)
Mixed	10 (9.8)
Cancer Subtype	
ER + HER2-	35 (34.3)
ER-HER2-	24 (23.5)
HER2+	43 (42.2)

Variables

Protocol characteristics

Exclusion criteria that were analyzed included vital signs, laboratory values, and comorbid conditions. Vital signs included systolic and diastolic blood pressure. Laboratory values included alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin, neutrophil count (ANC), platelets, hemoglobin (Hgb), and Eastern Cooperative Oncology Group (ECOG) performance status. Comorbid conditions included prior cancer diagnoses, human immunodeficiency virus (HIV), cardiovascular disease, presence of central nervous system (CNS) metastases and congestive heart failure. Prior cancer diagnosis and cardiovascular disease were further analyzed as time since exacerbation to mirror guidelines within the protocols.

Statistical analysis

Frequencies and percentages were reported for categorical variables using SAS© software, version 9.4 (SAS Institute, Cary, NC).

Results

Sample characteristics

A total of 102 protocols were included, which differed substantially in exclusion criteria. Most protocols did not include exclusionary parameters for blood pressure; 24% included an upper limit for systolic blood pressure and 23% included an upper limit for diastolic blood pressure. Most protocols included lab-based parameters, although substantial heterogeneity was observed. Within liver laboratory values, 78% included specific limitations for ALT, 80% for AST, and 78% for bilirubin. For ALT, 6 different cut points, ranging from the institutional upper limit of normal (ULN) to 3xULN were used, with frequency of use as low as 2% for ULN to as high as 40% for 2.5x ULN. Similar variability was observed for AST. For bilirubin, 9% used ULN, 2% used 1.2xULN, 3% used 1.25xULN, 56% used 1.5xULN, 6% used 2xULN, and 2% used 3xULN (Fig. 1A). For hematological labs, exclusions included a lower limit for ANC (81%), hemoglobin (72%), and platelets (81%). The specific limits for ANC ranged from 500-1800mcL, 8–10 g/dL for hemoglobin, and 50,000-150,000mcL for platelets. The most common ANC lower limit used was 1,500mcL (n = 65), hemoglobin was 9g/dL (n = 56) and platelets was 100,000mcL (n = 71) (Fig. 1B-D).

Of the comorbid conditions, cardiovascular disease was excluded in 79% of protocols. Thirty-eight percent of protocols did not specify a time frame for an exacerbation. When included, 4% of protocols specified no acute exacerbation within the previous 3 months (4%), 32% within the previous 6 months, and 5% within the previous 12 months. Additionally, 49% excluded congestive heart failure. Exclusion for higher ECOG status was common (76% of protocols). A status over 1 (49%) was the most common exclusionary parameter and a status over 3 (1%) the least common parameter. History of a prior cancer was excluded in 66%, with most requiring no prior cancer within the previous 5 years (47%). Only 2% did not specify a time frame (Table 2). CNS metastases was included in 59% of protocols. The language varied between protocols, with some specifying “symptomatic” or “progressive” metastases while other

protocols excluded all participants who had any current or history of CNS metastases. Patients with a diagnosis of HIV were excluded in 6% of protocols (Table 2).

Table 2
Exclusion criteria: comorbid conditions

	Frequency (%) N = 102
Congestive Heart Failure	
Included	50 (49)
Not Included	52 (51)
Cardiovascular Disease	
Acute exacerbation in last 12 months	5 (4.9)
Acute exacerbation in last 6 months	33 (32.4)
Acute exacerbation in last 3 months	4 (3.9)
No specified time frame	39 (38.2)
Not included	21 (21)
Human Immunodeficiency Virus (HIV)	
Included	6 (5.9)
Not Included	96 (94.1)
CNS Metastases	
Included	60 (59)
Not Included	42 (41)
Prior Cancer	
Within previous 2 years	5 (4.9)
Within previous 3 years	12 (11.8)
Within previous 5 years	48 (47.1)
No specific time frame	2 (2)
Not Included	35 (34.3)
ECOG status	
0–1	50 (49)
0–2	27 (26.5)
0–3	1 (0.9)
Not included	24 (23.5)

	Frequency (%) N = 102
Systolic Blood Pressure	
Included	24 (23.5)
Not Included	78 (76.5)
Diastolic Blood Pressure	
Included	23 (22.6)
Not Included	79 (77.5)

Discussion

We observed substantial heterogeneity in exclusion criteria across laboratory values and comorbid conditions within breast cancer clinical trials. The observed heterogeneity, coupled with the lack of justification for these specific thresholds, calls into the question the need for using these arbitrary values. While patients with abnormal laboratory results are often excluded from clinical trials due to concern for organ dysfunction [8], it has been shown that patients with AST/ALT > 5-10xULN and bilirubin > 2.5-5xULN may be asymptomatic and take doses of hepatically metabolized drugs equivalent to patients with no abnormalities [8]. Furthermore, the targets for ANC may not be appropriate. Patients of African descent may have benign ethnic neutropenia, with baseline ANC values less than 1500 without associated risk of infection [11]. The lack of careful consideration for thresholds needed to protect patients may not only limit generalizability, but also exacerbate disparities.

Exclusion criteria for comorbid conditions are equally heterogenous and lack standardization. Previous research has noted a lack of evidence to guide treatment in patients with cancer who have cardiovascular disease, a notably increasing population, which is the result of clinical trials excluding this population [12]. Exclusions based on cardiac disease primarily affect the older population, decreasing their enrollment by about 5% [13]. While some drugs have cardiotoxic effects, these exclusion criteria should be based on drug-specific toxicities and not on blanket statements based off the patient's previous acute exacerbation. Additionally, protocols that included criteria pertaining to a patient's history or presence of CNS metastases should be in accordance with the July 2020 U.S. Food and Drug administration guidelines, which advises against blanket exclusion of patients with CNS metastases [14].

We support the efforts of the ASCO and Friends of Cancer Research and the FDA to broaden eligibility criteria and recommend further research to find an appropriate standard upper or lower limit for laboratory values, with drug-specific considerations. We also recommend research to determine the appropriate amount of disease burden that can be allowed for patients that have comorbid conditions, rather than arbitrarily mandating disease-free time frames. These steps are necessary to ensure that

eligibility criteria do not unnecessarily restrict patient enrollment. We advocate for an inclusive mindset that would require investigators to provide protocol-specific scientific reasoning for eligibility criteria.

Several limitations should be considered. This study does not account for the type of medications used in the trial and potential for specific adverse effects that may impact choice of exclusion criteria. Some protocols may have been unintentionally excluded in our review due to a transition of software UAB used to track clinical trial protocols in 2016. Additionally, only breast-specific clinical trials were used in this study. However, given that these criteria are not breast-cancer specific, we anticipate this to be applicable across other cancers.

Conclusion

Substantial heterogeneity was observed in clinical trial protocols. While eligibility criteria exist to protect participants, there is a lack of evidence for current parameters. This is concerning when prior research has shown the effect restrictive eligibility criteria has on trial enrollment and drug generalizability [2, 5, 12]. Further research is needed to determine specific exclusion criteria that is generalizable while allowing for agent-specific concerns.

Declarations

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Conflicts of Interest: Dr. Rocque received research funding from Genentech, Pfizer, and Carevive and consulting fees for Genentech and Pfizer. The other authors have no conflicts of interest to disclose.

Availability of data and material: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code Availability: The code during the current study is available from the corresponding author on reasonable request.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the University of Alabama at Birmingham Office of the Institutional Review Board for Human Use (IRB-300001910) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to Participate: Informed consent was obtained from all individual participants included in the study.

Consent for Publication: Consent was obtained from all authors included in the study.

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Figures

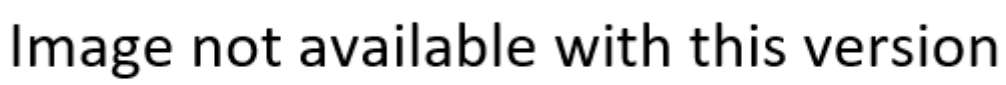

Figure 1

a-d Liver and hematologic laboratory exclusion criteria limits