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Evolution in the eligibility criteria of randomized controlled trials for systemic cancer therapies

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ABSTRACT

Background: Eligibility criteria in randomized controlled trials (RCTs) reduce inter-patient heterogeneity, but may reduce generalizability of results. Here, we explore temporal changes in eligibility criteria of practice-changing RCTs for systemic cancer therapies and in the proportion of patients excluded from these trials after application of eligibility criteria.

Methods: An electronic search identified practice-changing RCTs published in six major journals between July 2010 and December 2012. Trial protocols were identified through journal websites and communication with authors or study sponsors. Eligibility criteria were extracted from protocols. The number of patients excluded after application of eligibility criteria was extracted from the CONSORT diagrams and text of publications. Changes in eligibility criteria over time were assessed by logistic regression and meta-regression was carried out to evaluate the impact of year of protocol on the proportion of patients who were excluded after screening.

Results: Eighty-six protocols written between 1987 and 2012 were included. Over time, there has been an increasing frequency of exclusion of patients with prior cerebrovascular events (OR 1.34, $p = 0.003$), coagulation/bleeding disorders (OR 1.34, $p = 0.006$), prior gastrointestinal bleeding (OR 1.33, $p = 0.01$), cardiac co-morbidities (OR 1.24, $p = 0.004$) and exclusion based on concurrent medication (OR 1.19, $p = 0.01$). There has been a decrease in upper age limit usage (OR 0.83, $p = 0.01$) and leukopenia (OR 0.83, $p = 0.009$). The proportion of patients excluded from trials has increased from 9% prior to 2000 to 18% after 2010 (p-value for trend <0.001).

Conclusions: RCTs have become less representative of cancer patients treated in routine practice with increased use of organ-specific and co-morbidity-based exclusion criteria.

Background

Randomized controlled trials (RCTs) provide the gold standard investigation for medical interventions. Eligibility criteria in RCTs allow for the inclusion of a homogenous study population [1], which increases accuracy of the effect of treatment. An undesirable effect of the application of eligibility criteria is that data from RCTs, although providing critical evidence of clinical activity, may not provide adequate information to judge the impact of new treatments when used in the real world setting [2].

It is well recognized that patients with advanced age or greater comorbidities are underrepresented in clinical trials [3,4]. However, there are inconsistent data about whether results of RCTs translate to similar findings in clinical practice. Some data show that compared to RCTs, less benefit and greater toxicity are observed when the same treatment is applied in general clinical practice [5], especially to older patients or those with greater comorbidities than trial participants [6]. Other data show similar magnitudes of effect in RCTs and in clinical practice [7].

Differences observed in efficacy and toxicity of a particular type of therapy in patients treated in RCTs and in routine practice may result from the application of stringent eligibility criteria in RCTs.

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The evolution of eligibility criteria over time is not well studied. Furthermore, a lack of clarity remains as to whether eligibility criteria are based on prior pre-clinical or clinical experience with investigational agents.

We hypothesized that there has been increasing use of eligibility criteria in practice-changing RCTs over time and that this trend would not be explained by prior safety data with respective drugs. Here, we report on a study exploring the temporal changes in eligibility criteria in RCTs evaluating systemic cancer therapies and the association between these eligibility criteria and known drug label safety reports.

Methods

Data sources

A search of all articles published between July 2010 and December 2012 in the New England Journal of Medicine, The Lancet, Journal of the American Medical Association, Lancet Oncology, Journal of Clinical Oncology and the Journal of the National Cancer Institute was performed to identify articles reporting results of RCTs in adult patients with solid tumors. These journals were selected as they are considered to publish a high proportion of practice-changing RCTs in clinical oncology and have a policy of requiring the publication of protocols as a condition of acceptance of articles. Supplementary sections of articles were accessed to obtain the trial protocol when available. When not available, the editorial offices were contacted by email to request copies of the protocol; if this was not successful the corresponding author or the sponsor was contacted.

For our analysis, we included all two-arm, superiority randomized phase II and phase III RCTs reporting results of experimental systemic cancer therapies. Biomarker studies, reports of non-randomized trials, phase I/II trials, trials of radiation therapy or surgery and trials comparing drug sequences were excluded. This selection process ensured reasonable homogeneity in the sample of RCTs, thereby leading to an expectation of normally distributed standard errors for measured parameters.

For each approved experimental agent studied in an eligible trial, we also accessed the U.S. Food and Drug Administration (FDA) website [8] and extracted data on all known adverse reactions and warnings for the respective drugs.

Data collection and variable definition

Data were extracted using a prospectively defined electronic data extraction sheet by two independent authors (AS and RG). Discrepancies were resolved by a third author (EA). Extracted variables included: year of protocol (defined as most recent date listed on the available protocol), year of initiation of accrual, year of completion of accrual, trial sample size, phase of trial, disease site, trial funding, type of systemic agent (targeted agent, chemotherapy, immunotherapy, hormonal therapy or other), highest allowable Eastern Cooperative Oncology Group (ECOG) performance status, the presence of a lower age limit, the presence of an upper age limit, minimum anticipated life expectancy, requirement for measureable disease and exclusion of patients with serious and/or unstable medical conditions, co-morbidities or specific concurrent medications. Finally, we consulted the Consolidated Standards of Reporting Trials (CONSORT) figure and text of the publication of each study and extracted the number of patients excluded from each study after application of eligibility criteria.

Co-morbidities were defined by organ system, specifically: cardiac, hepatic, renal, hematological, coagulation, neurological, pulmonary, gastrointestinal, inflammatory and endocrine. Within each system, eligibility criteria were assessed for exclusion of specific co-morbidities and the cut-off used to define the co-morbidity. Table A.1 shows the definitions of all co-morbidities. Data on exclusion of specific concurrent medications comprised the presence of an exclusion criterion to any of the following medications: cytochrome P450 inducer or inhibitor, agents associated with QT prolongation, corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), herbal medication or the term 'other drugs'.

Additionally, for each approved experimental drug studied in at least one of the study protocols, we extracted the presence of FDA warnings and FDA documentation of adverse reactions from the drug label.

Statistical analysis

Descriptive statistics were utilized to summarize characteristics of evaluated protocols. The influence of time on the presence or absence of an eligibility criterion was evaluated using logistic regression with year of protocol as the predictor variable of interest. To account for the potential for accrual time to confound results, the analysis was then repeated with year of completion of accrual replacing year of protocol. Sensitivity analyses were conducted to explore the influence of drug class on results by including only protocols for targeted agents, the influence of stage of cancer by including only protocols for metastatic tumors (excluding adjuvant/curative therapy) and including only protocols dated between 2000 and 2010, thereby excluding outliers. Evaluation of the influence of time on the cut-off used to define a co-morbidity was explored using simple linear regression. Univariable logistic regression was also utilized to assess the relationship between presence of FDA drug label safety warnings and adverse reactions with the presence of related eligibility criteria in the study protocol evaluating the specific experimental agent. Meta-regression comprising a logistic regression weighted by study sample size was carried out to evaluate the impact of year of protocol on the proportion of patients excluded from trials after application of eligibility criteria. Statistical analyses were performed using SPSS version 21 (IBM Corp, Armonk, NY). Statistical significance was two-sided and defined as $p < 0.05$. A step-up controlling procedure (Benjamini–Hochberg method) was utilized to adjust for multiple hypothesis testing ensuring the false discovery rate (FDR) was below a nominal level of 0.05 [9].

Results

Study characteristics

Of the 399 articles identified initially, 200 met the eligibility criteria and 86 protocols were available for analysis (see Fig. 1 and Table A.2). Of these, 56 (65%) were available from journal websites, 28 (33%) were provided by corresponding authors and 2 (2%) were provided by the study sponsor. Available protocols were dated between 1987 and 2012. No difference was identified in the study characteristics between available and unavailable protocols (Table A.3).

Characteristics of included studies are shown in Table 1. Older studies were more likely to have longer duration of accrual (p-value for trend <0.001) and to be adjuvant trials; 86% of studies prior to 2000 were in the adjuvant/curative setting whereas 33% of studies after 2010 were in the adjuvant/curative setting (p-value for trend 0.005). There were no temporal relationships with the probability of a positive versus negative trial (p-value for trend 0.55) or with the proportion of U.S. versus non-U.S. trials (p-value for trend 0.12).