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Attitudes towards open-label versus placebo-control designs in oncology randomized trials: A survey of medical oncologists

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Abstract

Rationale, Aims and Objectives: Randomized trials are considered the gold standard when assessing the efficacy of new therapeutic agents. In clinical situations where no standard of care therapy is approved, randomized trials usually compare experimental agents to either a placebo or an open-label nonintervention arm (i.e., best supportive care). We surveyed Canadian medical oncologists to understand their attitudes towards each design.

Methods: Members of the Canadian Association of Medical Oncologists were invited to participate in an anonymous online survey. Standardized case scenarios were used to determine participants' attitudes regarding the role of open-label versus placebo-controlled trials.

Results: A total of 322 medical oncologists and trainees were invited to participate and 86 responded (response rate 27%). Fifty-one (59%) believed that open-label trials are an acceptable alternative to placebo-controlled design when investigating a therapeutic agent in the adjuvant setting. Thirty-eight (49%) deemed it acceptable to compare the investigational agent to an open-label arm instead of a placebo to assess progression-free survival in the metastatic setting. Twenty-eight (38%) of respondents felt that open-label design was acceptable when assessing the quality of life endpoint. Most physicians were unsure whether the US Food and Drug Administration require a placebo-controlled arm in oncology trials.

Conclusion: Canadian medical oncologists participating in this survey are divided in their opinions regarding the acceptability of an open-label design in randomized-controlled trials, where no standard therapy is approved. Clearer guidance from regulatory bodies on the adequacy of different trial designs is needed.

KEYWORDS
evidence-based medicine, medical ethics, medical research

1 | INTRODUCTION

Properly conducted, randomized controlled trials (RCT) are considered the gold standard study design to assess the efficacy of any new pharmaceutical agent.[1] Placebo-controlled trials are important because they help to differentiate between the benefits and safety of an experimental treatment versus those associated with the placebo effect or patients' underlying disease.[2] However, this trial design is considered ethical if no efficacious comparative treatment is available and participants receiving the placebo are not subjected to any additional risk of serious or irreversible harm.[1,3,4]

Due to variations in reporting of symptoms, a placebo arm can be especially important in trials assessing subjective endpoints such as relief of pain. Unfortunately, in addition to missing any potential benefit of the investigational treatment arm, patients randomized to the placebo arm often suffer inconveniences of being on placebo including travel expenses, multiple appointments, work absence and loss of income and venipuncture.[5,6]

An open-label noninterventional arm (i.e., best supportive care) can be an alternative to a placebo arm in clinical trials when no effective comparative therapy is available.[7] Noninterventional arm trials limit unnecessary inconveniences to patients as opposed to placebo-controlled trials and are more appealing to patients, which in turn may improve recruitment, though at the expense of important internal validity considerations. Additionally, they may offer a more affordable alternative to a placebo-controlled trial.[8,9]

There is currently a lack of consistency observed in oncology clinical trials, with trials assessing similar endpoints with different designs. For example, adjuvant atezolizumab was assessed in both urothelial carcinoma (IMvigor010, NCT02450331)[10] and renal cell carcinoma (IMmotion010, NCT03024996): the latter used a double-blinded, placebo-controlled design, whereas IMvigor010 used an observation open-label noninterventional arm design. Some practitioners might consider open-label as an invariably inferior trial design.[11] Therefore, in this study, we surveyed Canadian medical oncologists to assess their current attitudes towards open-label noninterventional arm versus placebo-controlled design in oncology clinical trials.

2 | MATERIALS AND METHODS

In 15 May 2019, members of the Canadian Association of Medical Oncologists (CAMOs) received an electronic invitation to participate in an anonymous online survey. Members were contacted through the CAMO electronic mailing list and provided with a hyperlink to an anonymous online survey linked to a secure database (SurveyMonkey Inc.). An E-mail reminder was sent to potential participants two weeks after the initial invitation.

The survey themes and questions were developed, drafted and reviewed by clinicians and researchers with expertize in medical oncology, clinical trials and survey design from the Ottawa Hospital Research Institute and from the Ottawa Hospital Cancer Centre, Ottawa, Ontario, Canada. To add validity, the survey draft was piloted among 10 medical oncologists from the Ottawa Hospital Cancer Centre, Ottawa, Canada. The results were reviewed and changes were made to make the final survey clearer and conciser.

We assessed whether responders consider an open-label design an acceptable or preferable alternative to a placebo-controlled arm using three standardized case scenarios: Scenario A—adjuvant RCT with overall survival (OS) as the primary endpoint, Scenario B—RCT in palliative patients, with progression-free survival (PFS) as the primary endpoint, and Scenario C—RCT in palliative patients, with quality of life as the primary endpoint (Table 1). Responders' reasons to prefer one design over the other in each scenario were further evaluated. In addition, the survey consisted of questions assessing responders' demographics and their attitude towards recruitment of patients to clinical trials with an oral or intravenous placebo arm, whether any of their patients declined participating in a clinical trial because they were afraid of being randomized to a placebo arm, and whether they believe an open-label design would result in higher patient dropout.

Survey responses were summarized with frequencies and percentages. χ^2 Or Fisher's exact tests were used to assess the association between participants' attitude towards the use of a noninterventional arm in the various scenarios, and each of the following variables: number of years in practice (<10 vs. ≥10), sex, place of work (academic, university-affiliated vs. community practice), and number of patients they recruited to clinical trials in the last year (≤5 vs. >5). A p-value of less than 0.05 was used for statistical significance. A $5 Starbucks voucher was offered upon completing the survey. The survey was approved by the Ottawa Health Science Network Research Ethics Board.

TABLE 1 Standardized case scenarios used in the survey

Scenario A	A 52-year-old male patient diagnosed with cancer Y is being enrolled in an adjuvant study of agent X with a primary endpoint of overall survival. Agent X is known to be active in the metastatic setting for cancer Y. There is no standard adjuvant therapy for cancer Y
Scenario B	A 64-year-old female patient with metastatic cancer Y has exhausted all standard therapies. She is being enrolled in a phase III study for agent Z with a primary endpoint of progression-free survival. Agent Z is known to be active in phase II for cancer Y
Scenario C	A 64-year-old female patient with metastatic cancer Y has exhausted all standard therapies. She is being enrolled in a phase III study for agent Z with a primary endpoint of the patient's quality of life assessment. Agent Z is known to be active in phase II for cancer Y

TABLE 2 Demographics of the physicians answering the survey

Demographic	Physicians *N* (%)
Years practising as a medical oncologist	
<10	33 (38)
10–20	20 (23)
>20	21 (24)
Medical oncology resident/fellow	12 (14)
Sex	
Male	43 (50)
Female	41 (48)
Preferred not to answer	2 (2)
Practice setting	
Academic (university-affiliated)	81 (94)
Community	5 (6)
Primary oncology focus of practice	
Breast	41 (48)
Lung	35 (41)
Gastrointestinal	40 (47)
Genitourinary	28 (33)
Central nervous system	11 (13)
Sarcoma	14 (16)
Melanoma	16 (19)
Other	29 (34)

TABLE 3 Tests of association between participants' acceptance of an open-label design and various demographic variables

	Percentage of responders agreeing that an open-label design is acceptable		
	Scenario A	Scenario B	Scenario C
Sex			
Male	67%	50%	37%
Female	51%	46%	40%
p Value	0.13	0.72	0.78
Number of years in practice			
<10	58%	50%	42%
≥10	61%	47%	33%
p Value	0.76	0.82	0.44
Number of patients responder recruited to clinical trials in the last year			
≤5	63%	48%	38%
>5	57%	49%	38%
p Value	0.64	0.95	0.17
Place of work			
University-affiliated	57%	48%	39%
Community practice	100%	60%	25%
p Value	0.08	0.67	1

3 | RESULTS

A total of 322 Canadian medical oncologists and medical oncology trainees participated in the survey and 86 responded (response rate 27%). Participating physicians' demographics are summarized in Table 2.

3.1 | Scenario A: Adjuvant RCT with OS as a primary endpoint

In the adjuvant setting, 59% believed that it is acceptable to compare an investigational agent to an open-label rather than a placebo. Among them, 65% believed that an open-label design is as reliable as a double-blind placebo-controlled design for this setting, while 35% preferred an open-label design due to concerns that might be associated with a placebo-controlled arm. In this scenario, 57% considered the results of a published study with an open-label design as valid as a blinded placebo-controlled design. No association was found between participants' acceptance of an open-label design in the adjuvant setting, and their number of years in practice (58% <10 years vs. 61% ≥10 years; $p = 0.76$), sex (67% male vs. 51% female; $p = 0.13$), place of work (57% university-affiliated vs. 100% community practice; $p = 0.08$), or number of patients recruited to clinical trials in the last year (63% ≤5 patients vs. 57% >5 patients; $p = 0.64$; Table 3).

3.2 | Scenario B: RCT in palliative patients, with PFS as the primary endpoint

Forty-nine percent of physicians answered that when assessing PFS in the metastatic incurable setting, it is acceptable to compare an investigational arm to an open-label rather than a placebo arm. Among them, 49% believed that an open-label design is as reliable as a placebo-controlled arm, whereas 51% preferred not to use a placebo-controlled arm due to concerns inherent to this design. In this scenario, 48% of participants would consider the results of an open-label study as valid as a blinded placebo-controlled design. No association was found between participants' acceptance of an open-label design in assessing PFS in the metastatic setting and their number of years in practice (50% <10 years vs. 47% ≥10 years; $p = 0.82$), sex (50% male vs. 46% female; $p = 0.72$), place of work (48% university-affiliated vs. 60% community practice; $p = 0.67$) or the number of patients recruited to clinical trials in the last year (48% ≤5 patients vs. 49% >5 patients; $p = 0.95$; Table 3).

3.3 | Scenario C: RCT in palliative patients, with quality of life as a primary endpoint

In Scenario C, 38% of participants thought that it is acceptable to use an open-label noninterventional arm instead of a placebo-controlled trial and 34% would consider the results of a published study with an open-label design as valid as a double-blinded placebo-controlled design. No association was found between participants' acceptance of an open-label design in assessing the quality of life in the palliative setting and their number of years in practice (42% <10 years vs. 33% ≥10 years; $p = 0.44$), sex (37% male vs. 40% female; $p = 0.78$), place of work (39% university-affiliated vs. 25% community practice; $p = 1$) or the number of patients recruited to clinical trials in the last year (38% ≤5 patients vs. 38% >5 patients; $p = 0.17$; Table 3).

Participants mentioned that the main disadvantages associated with a placebo-controlled trial design were patients' time commitment (49/73, 67%), difficulties recruiting due to patients' lack of interest (45/73, 62%), strain on limited public/clinic resources (43/73, 59%) and potential harm to patients (24/73, 33%). In contrast, 62% were concerned that an open-label design would result in a higher patient drop-out rate.

Most physicians agreed that an open-label design would improve patient recruitment. Twenty-seven percent mentioned that 20%–50% of their patients declined to participate in a clinical trial because they were afraid to be randomized to an oral placebo arm, whereas 34% reported that between 20% and 50% of their patients declined because they were afraid to be randomized to an intravenous placebo arm. Ninety-two percent of respondents felt comfortable recruiting patients to a study with an oral placebo-controlled arm, while 85% felt comfortable recruiting patients to a study with an intravenous placebo arm.

Most physicians answered that they are unsure whether the US Food and Drug Administration requires a placebo-controlled design in oncology clinical trials in a setting similar to the three scenarios described in this survey (61% for Scenario A, 70% for Scenario B, and 73% for Scenario C).

4 | DISCUSSION

Many patients dislike the possibility of placebo.[12] In our survey, many respondents acknowledged that a significant proportion of their patients had declined enrollment on a clinical trial because of the fear of being randomized to a placebo arm, especially when treatment is administered intravenously. Sixty percent of physicians agreed that using a noninterventional arm instead of a placebo arm would help recruitment. Yet, our survey demonstrated that many physicians believe that a noninterventional arm is not acceptable and they may not regard the results of such a study as reliable as those from a placebo-controlled RCT. The proportion of responders regarding an open-label noninterventional arm as an acceptable alternative increases when objective study endpoints with less potential confounders, such as OS, are used. It is plausible that the lack of clarity from regulatory bodies on the appropriateness of open-label noninterventional arm design contributes to the division in opinions observed in our survey. In fact, the majority of participants acknowledged not being aware of the US Food and Drug Administration's policies on placebo arm alternatives.

When no other efficacious treatment is available, an open-label noninterventional arm could be considered an acceptable alternative to a placebo arm. Open-label noninterventional arm design overcomes inherent disadvantages that placebo-controlled trials have on patients, such as the inconvenience, pain and possible harm associated with intravenously administered placebo. It can also mitigate some less obvious disadvantages of a placebo-controlled design such as more frequent medical appointments and related travel and time commitments. Frequent medical appointments are known to be associated with financial burden resulting from travel, lodging and childcare expenses and time lost from work, resulting in impaired quality of life.[5,13] However, open-label design can be associated with several limitations such as possible higher patient dropout, concerns regarding the internal validity of the study including possible patients underreporting of adverse events.[14] Some of these concerns can be mitigated by carefully designing the study. Investigators and stakeholders should be aware that an open-label noninterventional arm design should be restricted to studies with objective primary endpoints, such as OS, PFS or disease-free survival, which are less prone to biases resulting from investigator or patient expectations.[15] In addition, blinded independent central reviewers can be used to ensure objective evaluation of patient assessments such as imaging. This design is even more relevant when it is difficult to blind investigators from treatment allocation due to well-known or expected toxicity of the investigational agent.[16,17]

Our study has several limitations. It is a single country survey. There is selection bias, as not all Canadian medical oncologists are members of CAMO. In addition, it is possible that not all dependent variables could be evaluated using only three scenarios.

In conclusion, the results of our survey echo the current confusion associated with the use of a noninterventional arm open-label design versus a placebo, double-blind design in oncology clinical trials. We believe that this issue should be addressed by the regulatory bodies using unambiguous language to provide clear guidance to physicians and investigators.

CONFLICT OF INTERESTS

There are no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

All authors contributed significantly to the work. *Conceptualization*: Igal Kushnir, Mark Clemons, Dean Fergusson, Dominick Bossé, M. Neil Reaume. *Formal analysis*: Igal Kushnir. *Writing*: Igal Kushnir. *Reviewing and editing*: Igal Kushnir, Mark Clemons, Dean Fergusson, Dominick Bossé, M. Neil Reaume.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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