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Dose modification rules and availability of growth factor support: A cross-sectional study of head-to-head cancer trials used for US FDA approval from 2009 to 2021

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Abstract *Aim of the study:* Different drug modification rules or growth factor support guidance may affect the results in oncology randomised controlled trials. We aimed to estimate the prevalence of unequal rules for dose modification rules or the use of myeloid growth factors in head-to-head registration Food and Drug Administration trials.

Methods: This cross-sectional analysis included all head-to-head registration randomised controlled trials leading to a US Food and Drug Administration approval between 2009 and 2021. Trials examined anti-cancer drugs in the advanced or metastatic setting where a comparison could be made between arms regarding either dose modification rules or myeloid growth factors recommendations. Sixty-two registration trials met inclusion criteria. Information abstracted for each trial included tumour type, setting, phase, and type of sponsor. We assessed, according to pre-specified rules, imbalance in drug modification rules, myeloid growth factors recommendations or both.

Results: We find 40 of 62 (65%) selected trials have unequal rules for dose medication, granulocyte colony-stimulating factor (G-CSF) use or both. Six trials (10%) had rules favouring the control arm, while 55% of selected trials (34/62) favoured the experimental arm. Among these, 50% (17/34) had unequal drug modification rules, 41% (14/34) had unequal G-CSF rules and 9% contained both (3/34).

Conclusion: We find that 55% of trials testing anti-cancer drugs against each other used protocol rules that favoured the experimental arm. This leaves open the question of whether new molecules are truly superior to older molecules or if instead different outcomes are due to

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more aggressive dosing or growth factor support. Trials should utilise equal rules for dose medication and G-CSF support.

1. Introduction

Comparative effectiveness studies are vital in oncology, where there are many treatment options that extend or enhance life. Head-to-head randomised controlled trials (RCTs) are now estimated to constitute just under 10% of all RCTs [1].

Imbalances may occur that threaten the reliability of these studies. These have been called 'hard-wired biases', as they often cannot be adjusted for post hoc and can only be acknowledged [2]. Examples include trials that compare new drugs to older, antiquated therapies, which are no longer in favour, a problem increasingly referred to as an inappropriate or straw man control arm [3−5]. Trials may appropriately or inappropriately utilise crossover, which affects downstream endpoints, such as first-progression-free-survival (PFS1) [6]. An under-recognised threat to the validity of comparative effectiveness trials is unequal rules for dose reduction and the use of growth factor support.

In a fair head-to-head trial, rules for dose modification and the receipt of supportive or ancillary medications, such as granulocyte colony-stimulating factor (G-CSF), would be balanced. This permits the trial to isolate the relative value of the experimental compound versus the control arm compound. In other words, dose reductions would occur similarly based on precipitating events, be of equal magnitude, and investigators should be permitted to or encouraged to use G-CSF at a similar juncture in both arms, if we wished to know which drug is superior. In the absence of this, results might be due to the effect of the new drug, or alternatively, the difference may be due to more aggressive drug dosing or better support.

Unequal drug dosing and the potential impact on outcomes have been described previously, though this work was not empirical [7]. Here, we sought to estimate the rate of imbalance in dose modification rules or use of myeloid growth factors in all head-to-head registration Food and Drug Administration (FDA) trials from 2009 to 2021.

2. Methods

2.1. Study design and research strategy

Ours was a retrospective, cross-sectional study that included all anti-cancer drugs approved by the FDA from January 2009 through December 2021. We adhered to Strengthening the Reporting of Observational studies in Epidemiology (STROBE) reporting guidelines.

2.2. FDA approvals identification and selection

Selected approvals needed to be anti-cancer treatments. The search was conducted using the FDA website and a previous cross-sectional analysis [8]. We reviewed each approval via the FDA website and retrieved trial data from the published results (located via the National Clinical Trial identifier).

Searches were performed on 20 February 2022. Because we used publicly available data and did not involve human subjects research, in accordance with 45 CFR §46.102(f), we did not submit this study to an institutional review board or require informed consent procedures.

2.3. Inclusion and exclusion criteria

We chose drugs approved based on (1) a comparative head-to-head RCT that examined an anti-cancer drug (2) in the advanced or metastatic setting.

The exclusion criteria were (1) trials not evaluating direct anti-cancer interventions (supportive care measures, infection mitigation preventions, or different stem cell mobilisation strategies); (2) non-comparative or non-randomised trials (phase 1 trials, single-arm studies, non-comparative randomised trials, trials with more than two arms); (3) approvals based on studies that combined multiple RCTs; (4) paediatric trials; (5) trials comparing the same agent with different route of administration; (6) trials where the only difference between arms were a single add-on investigational agent.

2.4. Data abstraction

Information abstracted for each approval included date of approval; name of the trial on which the approval was based; National Clinical Trial number; tumour type; setting; design (open or double blind); phase of the trial; experimental arm compound(s); control arm compound(s); and for each compound (experimental and control arm), we abstracted: planned doses within the trial, dose modification rules within the trial, doses in the FDA labels and dose modification rules in the FDA labels. We also abstracted primary outcome of the trial; the report of positive and statistically significant progression-free-survival (PFS) results (yes, no); the risk

of febrile neutropenia in cytotoxic regimens (see below); recommendation of growth factor (yes/no) and classification (see below), sponsor (industry, mixed of cooperative and industry, public).

In trials found to have unequal dose modifications rules (see below), we collected data on proportion of patients presenting a dose reduction, and proportion of patients with discontinuation due to an adverse event, in both arms.

Data related to the drug, the cancer type, and the approval basis were extracted from FDA labels, review documents, package inserts. Other data were extracted from the trial publication and the protocol, when available.

2.5. Mechanism of action of each trial's treatment arm

We classified the mechanism of action for every arm of the selected trials in five broad pharmacological categories: kinase inhibitors, monoclonal antibodies, cytotoxic chemotherapy, combination (being for instance a combination of monoclonal antibody and kinase inhibitor) and others.

2.6. Myeloid growth factors classification

Myeloid growth factors, comprising granulomacrophagic colony-stimulating factors (GM-CSF) or granulocyte colony-stimulating factors (G-CSF), are supportive treatment that may be used with myelosuppressive agents. Based on the risk of expected febrile neutropenia and according to guidelines, they can be prescribed as primary prophylaxis, meaning since the first cycle, or secondary prophylaxis (after any occurrence of febrile neutropenia), or during the therapeutic phase of patients with febrile or prolonged neutropenia [9,10].

For each myelosuppressive agent or combination of agents (mostly cytotoxic chemotherapy), we classified the risk of febrile neutropenia based on international recommendations between high risk ($>20\%$), intermediate risk (between 10 and 20%) and low risk.

We identified five types of growth factor recommendations: (1) no mention in the protocol; (2) not allowed; (3) discouraged; (4) possible utilisation, left at the discretion of the physician but not mandatory; and (5) mandatory *per* protocol rules.

We compared rules in treatment groups according to the risk of febrile neutropenia, which may have differed between arms. We concluded an 'imbalance' in trials with one arm with intermediate- or high-risk agents and where G-CSF was either not mandatory or prohibited in case of haematological toxicity. In instances of intermediate or high-risk neutropenia in both arms, we looked for any potential specific imbalance into the protocol between arms, and otherwise coded either 'no detected imbalance', either 'indeterminate' when no rules could be found. The absence of recommendation

of G-CSF in low-risk neutropenic regimens was not considered as penalising these regimens.

2.7. Modification rules classification

We compared, when possible, the dose modification rules between arms and assessed three factors.

1) The number of dose reductions allowed before stopping the drug. Fewer steps potentially penalise one treatment group because the treatment may theoretically be stopped earlier in the case of recurring toxicity. In the case of combination therapy, the steps were counted for every drug. For example, if the treatment was a combination of cytotoxic agents and two steps were allowed for one drug and one step for the other, the number of dose reduction steps for this group was counted as the average (1.5).
2) The existence of dose increasing rules. Lead-in periods or increasing the dose step-by-step allow for better tolerance and a potentially higher dose intensity (and efficacy). This may favour one arm if the other has no such rules. An exception was made for venetoclax, as the gradual increase of this drug, per-protocol, is justified by a very specific mechanism-of-action and toxicity profile with a high risk of tumour-lysis syndrome.
3) The percentage of the initial dose was coded for the first and second step of reduction, when present. This was done for each arm. For combination therapy, we coded the average of each compound, and if a step was not allowed for one compound, it was counted as a 0% of the initial drug dose in the average calculation.

Monoclonal antibodies have different pharmacokinetics properties (e.g., long half-lives) and usually wide therapeutic windows [11]. For these, dose modifications are rare and mostly replaced by delays or interruptions when necessary. Consequently, in combination treatment with monoclonal antibodies, they were not counted in this evaluation.

Based on these data, we concluded an imbalance in dose reduction rules between arms when either one or several rules of the following was seen: (1) an increase in dose was allowed in one arm only (favouring it); (2) a greater than 5-point-percent threshold was seen in the first dose reduction; (3) a greater than 5-percent-point threshold was seen in the second dose reduction; or (4) the number of steps was unequal (more steps favouring one arm).

When any discrepancy was noted, such as an increasing dose allowed in one arm but dose reduction favouring the other arm, we used hierarchical application of the rules described previously: rule 1 was prioritised over rule 2, which was prioritised over rule 3, followed by rule 4. Examples of such assessments are described in eMethod 1 (online supplement).

2.8. Classification of every FDA approval

Based on the data collected, we coded all approvals and their corresponding trials into four categories: (1)

favouring the control arm; (2) no detected imbalance; (3) favouring the experimental arm; or (4) indeterminate. We further coded the mechanism of imbalance, when present, into growth factors imbalance, dose modification rules imbalance or a combination of both.

TO made the selection and reviewed the FDA approvals for inclusion and abstracted the data for each approval. The data were reviewed by AH. Any questions were discussed between all authors and were adjudicated, when necessary, by VP.

2.9. Statistical analysis

Frequencies were calculated for categorical variables throughout. These statistical analyses were done using R version 3.6.2 (R Project for Statistical Computing) and a two-tailed P value less than 0.05 as the level of significance. We compared proportions with the Mann–Whitney U Test (Wilcoxon Rank Sum Test) when variables were not normally distributed.

3. Results

Between 2009 and 2021, we noted 441 FDA approvals, of which 62 met our inclusion criteria. The most common reasons for exclusion were non-randomised trial (n = 134) and studies that solely added on an additional agent (n = 111). eFig. 1 (online supplement) is a flowchart that details the approval selection process and reasons for exclusion.

Among trials supporting eligible approvals, 59 were phase 3 trials (of 62, 95%), and 3 were phase 2 trials. The design was open label in 59 of them (95%) and blinded in 3 (5%). The protocol was available for 48 trials (77%) but not for 14 (23%). Other study qualities are described in Table 1.

We detected an imbalance favouring the experimental arm in 34 of 62 trials (54.8%). An imbalance favouring the control arm was found in six trials (9.7%). No detected imbalance was found in 14 trials (22.6%), and our evaluation concluded an indeterminate assessment in eight trials (12.9%). Table 2 summarises these results.

Among trials where the control arm was favoured, the mechanism of imbalance was drug dose modification rules for all six trials. Among trials where the experimental arm was favoured (n = 34), the mechanism of imbalance was dose modification rules in 17 of 34 (50%), myeloid growth factor recommendations in 14 of 34 (41%), and a combination of both in 3 of 34 (9%). Fig. 1 illustrates the proportion and characteristics of all selected trials, with the mechanism of imbalance, when present.

In trials with unequal dose modification rules (n = 26), we found imbalances regarding the potential to increase the dose in 9 of 26 (35%) trials, the number of steps allowed in 17 of 26 (65%) trials and the

percentage of the initial dose for the first dose reduction in 20 trials (77%), or second dose reduction in 14 trials (54%). Some trials presented one or many of these features: Fig. 2 represents these data for both arms in each trial, when there were unequal dose rules favouring either the experimental (20) or control (6) arm.

Two of the six trials (33%) favouring the control arm were sponsored by cooperative groups, others were industry sponsored (66%). All trials (n = 34, 100%) favouring the experimental arm were industry funded. All but one trial with no detected imbalance were industry funded (21/22, 95.5%). These difference between groups according to the sponsor were significant (p = 0.002).

Among trials with unequal dose modifications rules, a median of 29.6% ((25th-75th percentiles = 17.30%–41.1%) of patients had a dose reduction. We also compared dose reduction and dose discontinuation rate between arms and found no significant differences (data not shown), which may be due to the limited number of trials for this analysis.

4. Discussion

We examined all head-to-head randomised trials leading to an FDA approval over a 13-year period and found unequal drug modification rules or myeloid growth factor recommendations in 65% of them (40/62). The imbalance favoured the control arm in six trials, while it favoured the experimental arm in 34 or 55% of all studies (34/62). Among these, 50% (17/34) had unequal drug modification rules, 41% (14/34) had unequal G-CSF guidance and 9% with both (3/34). There were strong relationships between funding source and bias favouring experimental arms.

Unequal dose reduction rules and their potential to impact outcomes have previously been noted, though no prior group has investigated the frequency of this phenomenon [7]. We found this problem is prevalent in head-to-head trials [42% of trials (26 of 62 studies)]. Moreover, nearly one in three patients end up on a dose besides the starting dose, making dose reduction a salient concern. We found several forms of unequal dose medication rules.

One example is different sized reductions. The PROfound trial investigated olaparib, as compared with either abiraterone or enzalutamide, in metastatic castration-resistant prostate cancer [12]. The first dose reduction in the olaparib arm was 83% (as compared with 75% in the control group), and the second reduction was 67% (as compared with 50% in the control group).

A second example is a difference in the number of steps allowed in dose reduction. In patients with untreated advanced hepatocellular carcinoma, lenvatinib was tested against sorafenib in a phase 3, open-label,

Table 1
Descriptive characteristics among trials with or without imbalance.

	Favour control (N = 6)	Favour experimental (N = 34)	No detected imbalance[a] (N = 22)	Total (N = 62)
Tumour type				
Acute leukaemia	0 (0%)	2 (5.9%)	1 (4.5%)	3 (4.8%)
Breast cancer	0 (0%)	3 (8.8%)	4 (18.2%)	7 (11.3%)
Chronic lymphocytic leukaemia	1 (16.7%)	2 (5.9%)	1 (4.5%)	4 (6.5%)
Chronic myeloid leukaemia	1 (16.7%)	0 (0%)	1 (4.5%)	2 (3.2%)
Colorectal cancer	0 (0%)	1 (2.9%)	0 (0%)	1 (1.6%)
Endometrial carcinoma	0 (0%)	0 (0%)	1 (4.5%)	1 (1.6%)
Oesophageal cancer	0 (0%)	2 (5.9%)	0 (0%)	2 (3.2%)
Gastro-oesophageal carcinoma	0 (0%)	1 (2.9%)	0 (0%)	1 (1.6%)
Hepatocellular carcinoma	0 (0%)	1 (2.9%)	2 (9.1%)	3 (4.8%)
Lymphoma T	0 (0%)	0 (0%)	2 (9.1%)	2 (3.2%)
Melanoma	1 (16.7%)	0 (0%)	3 (13.6%)	4 (6.5%)
Mesothelioma	0 (0%)	1 (2.9%)	0 (0%)	1 (1.6%)
Non-small-cell lung cancer	0 (0%)	13 (38.2%)	3 (13.6%)	16 (25.8%)
Prostate cancer	0 (0%)	1 (2.9%)	1 (4.5%)	2 (3.2%)
Renal cell carcinoma	2 (33.3%)	5 (14.7%)	2 (9.1%)	9 (14.5%)
Sarcoma	0 (0%)	1 (2.9%)	1 (4.5%)	2 (3.2%)
Urothelial carcinoma	1 (16.7%)	1 (2.9%)	0 (0%)	2 (3.2%)
Mechanism of action (experimental)				
Antibody drug conjugate	1 (16.7%)	4 (11.8%)	2 (9.1%)	7 (11.3%)
Chemotherapy	0 (0%)	1 (2.9%)	4 (18.2%)	5 (8.1%)
Combination[b]	2 (33.3%)	2 (5.9%)	3 (13.6%)	7 (11.3%)
Kinase inhibitor	3 (50.0%)	17 (50.0%)	7 (31.8%)	27 (43.5%)
Monoclonal antibody	0 (0%)	10 (29.4%)	6 (27.3%)	16 (25.8%)
Mechanism of action (control)				
Chemotherapy	3 (50.0%)	21 (61.8%)	13 (59.1%)	37 (59.7%)
Combination	0 (0%)	2 (5.9%)	2 (9.1%)	4 (6.5%)
Kinase inhibitor	3 (50.0%)	9 (26.5%)	4 (18.2%)	16 (25.8%)
Mixed	0 (0%)	0 (0%)	1 (4.5%)	1 (1.6%)
Monoclonal antibody	0 (0%)	0 (0%)	1 (4.5%)	1 (1.6%)
Other	0 (0%)	2 (5.9%)	1 (4.5%)	3 (4.8%)
Route of administration[c]				
IV vs. IV	1 (16.7%)	14 (41.2%)	10 (45.5%)	25 (40.3%)
IV vs. ORAL	0 (0%)	0 (0%)	3 (13.6%)	3 (4.8%)
IV vs. ORAL + IV	0 (0%)	1 (2.9%)	0 (0%)	1 (1.6%)
ORAL vs. IV	1 (16.7%)	8 (23.5%)	5 (22.7%)	14 (22.6%)
ORAL vs. ORAL	2 (33.3%)	9 (26.5%)	3 (13.6%)	14 (22.6%)
ORAL + IV vs. IV	1 (16.7%)	0 (0%)	1 (4.5%)	2 (3.2%)
ORAL + IV vs. ORAL	1 (16.7%)	2 (5.9%)	0 (0%)	3 (4.8%)
Setting				
First-line	4 (66.7%)	15 (44.1%)	9 (40.9%)	28 (45.2%)
Mixed	0 (0%)	1 (2.9%)	3 (13.6%)	4 (6.5%)
Second or subsequent	2 (33.3%)	18 (52.9%)	10 (45.5%)	30 (48.4%)
Sponsor				
Cooperative	2 (33.3%)	0 (0%)	1 (4.5%)	3 (4.8%)
Industry	4 (66.7%)	34 (100%)	21 (95.5%)	59 (95.2%)

[a] Including eight trials coded as 'indeterminate'.
[b] For example, monoclonal antibody plus kinase inhibitor.
[c] Experimental arm vs. control arm.

Table 2
All selected FDA head-to-head registration trials (n = 62), with number and proportion of (1) trials favouring the control arm, (2) with No detected imbalance and (3) favouring the experimental arm.

	Favour control	No detected imbalance[a]	Favour experimental	Total
Number of trials	6	22	34	62
Proportion	9.7%	35.5%	54.8%	100%

[a] Including eight trials coded as 'indeterminate'.

non-inferiority trial [13]. Not only was the first and second reduction imbalanced, favouring lenvatinib, but a third reduction was allowed only in the lenvatinib group [14]. As evidence that these rules allow for more dose intensity, the authors reported that patients in the lenvatinib group received 88% dose intensity of the planned starting dose and 83% in the sorafenib group despite comparable rates of dose reduction in the trial (37% had dose reduction on lenvatinib, and 38% had dose reduction on sorafenib) [13].
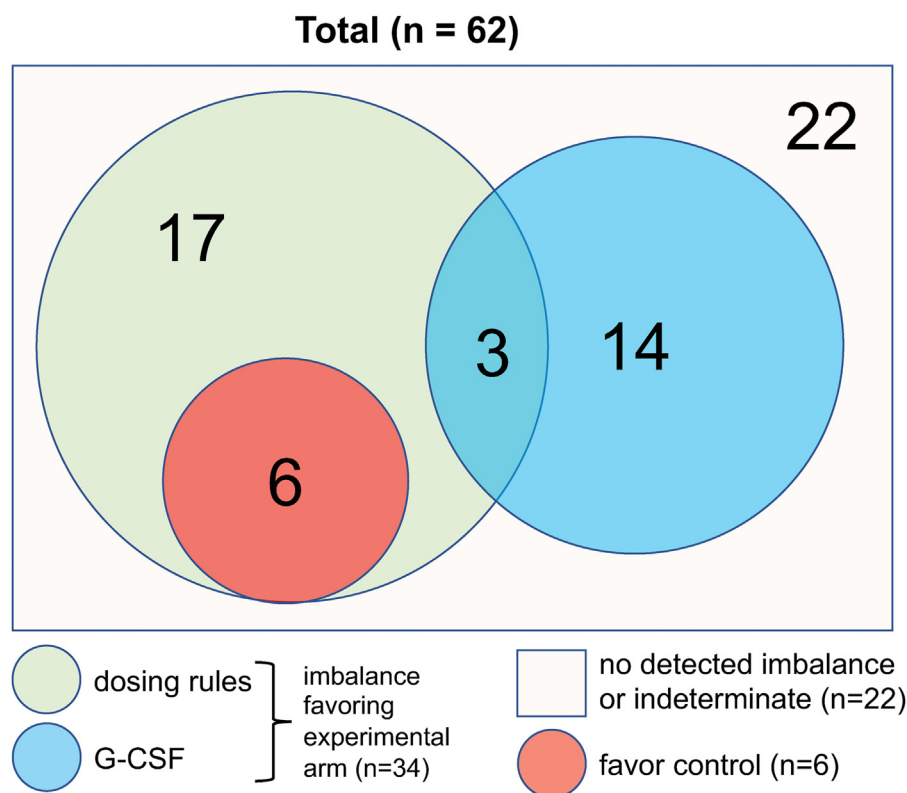
Total (n = 62)

Fig. 1. Venn diagram of all selected FDA head-to-head registration trials (n = 62), with mechanism of imbalance and favoured arm, when present (n = 40).

Myeloid growth factors may also affect cancer outcomes. Unequal or unfair rules raise the question of whether the control arm was adequately supported. One concern occurs in cases where there is an absence of 'mandatory' recommendations in intermediate to high-risk chemotherapy regimens, which is the standard of care in many nations. In trials run globally, including countries without ready access to G-CSF products, physician discretion may lead to an underuse of these agents or early withdrawal after toxicity. Consider now the KEYNOTE-042 trial, comparing pembrolizumab versus platinum-based chemotherapy in first line treatment in advanced or metastatic non-small cell lung cancers [15]. Patients treated with carboplatin AUC5-6 plus pemetrexed or paclitaxel 200 mg/m^2 were not allowed to receive prophylactic use of G-CSF, potentially enhancing toxicity and deteriorating outcomes.

Another example of unequal G-CSF support is when one arm mandates growth factors without reducing the dose for the next cycle in cases of first episode of febrile neutropenia, when the other arm has an immediate reduction in the next dose with no mandatory growth factor. We previously identified this feature design in the ASCENT trial, which was not immediately apparent, comparing sacituzumab govitecan to a restricted choice of monotherapy chemotherapies in patients with refractory metastatic triple-negative breast cancer [16]. This pushes dose intensity only in the experimental arm.

Our findings show most (55%) head-to-head cancer trials that bring new drugs to market have design features that favour the experimental arm. Of course, many of these agents are highly active and life prolonging and might have still yielded superior outcomes even if rules were equal; however, the existing literature does not tell us which drugs are better compounds and which drugs succeeded merely because of greater dose intensity. Oncologists and patients must be aware of this fact.

5. Limitations

Our work has limitations. First, there is uncertainty about the magnitude of impact from imbalance in drug modification rules or supportive treatment on clinical efficacy and outcomes. Our work primarily aims to identify where *per protocol* rules could be imbalanced, thus rendering possible bias, rather than quantifying the resultant bias. Without access to primary individual patient level data from many trials, the latter task is impossible. Second, one may argue that drug modification rules may differ because of pharmacological differences and does not reflect imbalance. We acknowledge this is possible, but if so, we should expect to see similar patterns in experimental and control groups for drugs of similar class formulation or mechanism, which we did not note. Third, another limitation
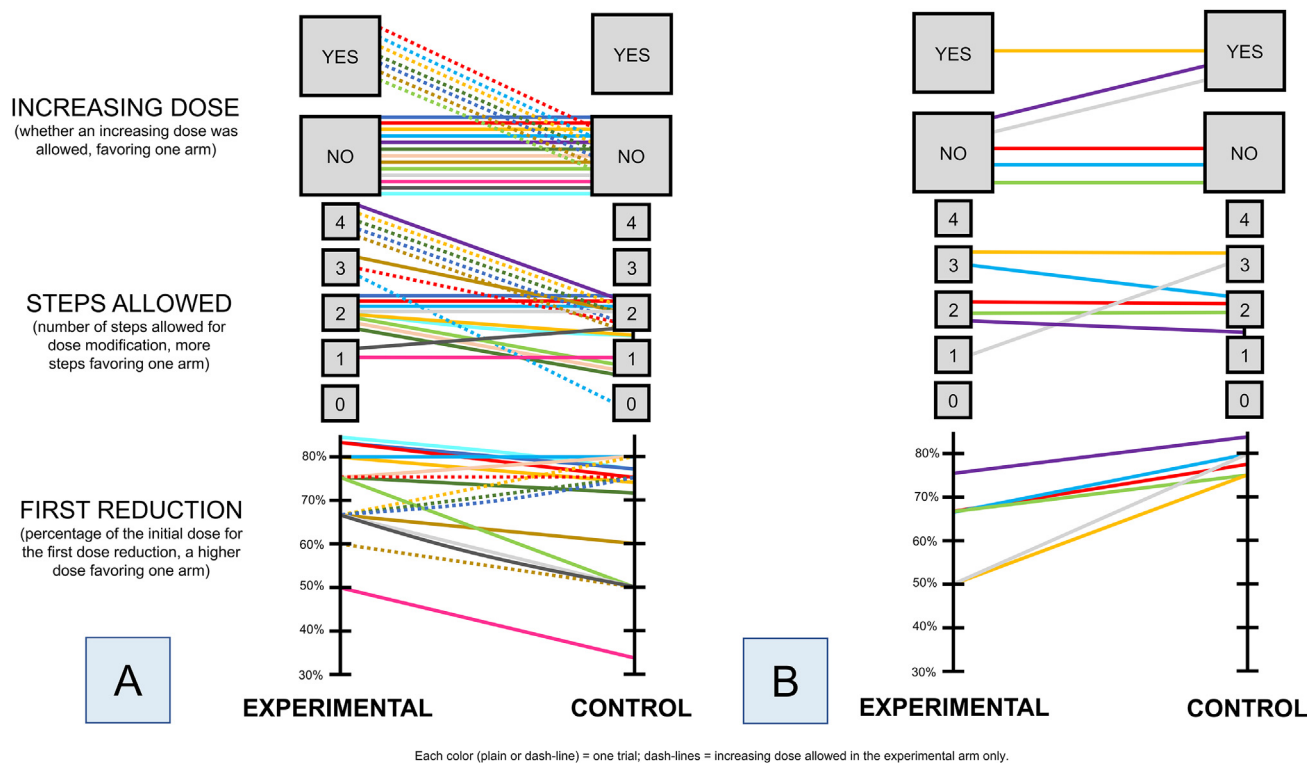
Fig. 2. Increasing dose, number of steps allowed, first level reduction, for each arm of FDA head-to-head registration trials with dosing rules imbalance. Legend: Panel A: Favour experimental (N = 20), panel B: Favour control (N = 6).

is that labels may restrict dose adaptation for approved drugs, which are more likely to be tested in the control arm. At the same time, these restrictions may serve as opportunities for other companies to test novel products in that space. Finally, we limited our study to a 13-year period of FDA registration trials. However, this is the first study to explore this research question with a wide methodological approach. We encourage others to expand this work.

6. Conclusion

We studied all drugs that received FDA approval based on comparison to a different active anti-cancer regimen. We found that 55% of these head-to-head trials had rules for dose modification or G-CSF support that favoured the experimental arm. Nearly one in three patients on trials with unequal dose modification rules had a dose reduction, making doses besides the starting dose relevant. It is impossible to know in all these cases whether the new drug is truly better than the old one, or if better outcomes were achieved by higher dose intensity. Future research should examine these agents, and reviewers should study trials for unequal drug dosing. Regulatory authorities should ensure that unnecessary imbalance in dose modification rules or growth factor support is avoided so that the control arm is not penalised.

Authors' contributions

VP contributed to the conception. TO, AH and VP contributed to the design of the study and statistical analysis plan. TO and AH collected the data. TO, AH and VP assembled the data and had accessed and verified the data. TO and AH did the statistical analyses. TO wrote first draft of manuscript, and all authors reviewed and revised the manuscript. All authors provided final approval of the manuscript.

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Role of the funding source

The funders had no role in the design and conduct of the study.

Conflict of interest statement

Vinay Prasad's Disclosures: Research funding: Arnold Ventures; Royalties: Johns Hopkins Press, Medscape; Honoraria: Grand Rounds/lectures from universities, medical centres, non-profits and

professional societies; Consulting: UnitedHealthcare; Speaking fees: Evicore; Other: Plenary Session podcast has Patreon backers. All other authors have no financial nor non-financial conflicts of interest to report.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.06.023.

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