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LETTER TO THE EDITOR

Response to Crevenna and Ashbury, Vallance and Bolam, and Crevenna and Keilani regarding the effects of exercise on chemotherapy-induced peripheral neuropathy

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Dear Editor,

We thank Drs. Crevenna and Ashbury [1], Drs. Vallance and Bolam [2], and Drs. Crevenna and Keilani [3] for bringing attention to the study of exercise for chemotherapy-induced peripheral neuropathy (CIPN) and for commending our recently published research [4]. The authors raise important points that indicate their expertise, their careful evaluation of our work, and their earnestness to advance the study and treatment of CIPN. We agree wholeheartedly that more high-quality research is needed in the study of CIPN and its treatment, including the use of exercise. We also agree with many of the limitations of our work that they described; in fact, we mentioned these limitations in the discussion section [4]. We are grateful for the opportunity to provide further information herein.

We agree with all commenting authors that our results *suggest* that exercise can attenuate the severity of CIPN symptoms; moreover, we agree that our conclusions are not definitive, as our work reflected an exploratory secondary analysis. We regret any confusion from our statement that exercise *reduced* the severity of CIPN symptoms compared to control, despite our statement being mathematically accurate. We agree that exercise *attenuated* increases in CIPN symptom severity compared to control over 6 weeks of chemotherapy. Moreover, our original manuscript already acknowledges increases in CIPN symptom severity in both exercise and control groups: "at post-intervention, patients in each condition reported more severe CIPN symptoms", which is also evident in Table 2 and Fig. 2 [4].

Next, we address Vallance and Bolam's methodological concerns [2], many of which we already raised as limitations (discussion, paragraph 5 [4]). First, regarding our outcome measures—the two 0–10 scales of numbness/tingling and hot/coldness in hands/feet—we agree to proceed with caution because these scales have not been tested as rigorously as a full questionnaire such as the CIPN-20 or FACT-Taxane. Second, Vallance and Bolam wrote, "The clinical meaningfulness of simply scoring > 0 is questionable and is not indicated in the literature" but also write, "Bao et al. proposed a score of ≥ 1 suggests mild symptoms, and scoring below one (< 1) is an indication of no symptoms," which is precisely what we did in our study as our 0–10 scale used integer values only (i.e., > 0 is identical to ≥ 1). Third, as requested, we report the prevalence of CIPN symptoms at both time points: for numbness and tingling, exercise increased from 24.7 to 36.5% (+ 11.8%), and control increased from 34.1 to 49.2% (+ 15.1%), yielding a net reduction of 3.4% by exercise (number needed to treat (NNT) = 29.7). For hot/coldness in hands/feet, exercise increased from 24.7 to 33.5% (+ 8.8%) and controls increased from 25.9 to 45.4% (+ 19.5%), yielding a net reduction of 10.6% by exercise (NNT = 9.4). These results suggest a small beneficial effect of exercise during chemotherapy on attenuating the incidence of CIPN symptoms. Fourth, Vallance and Bolam's suggestion of a Bonferroni correction to the false positive probability (alpha) underscores a broader point in the use of statistics in quantitative research. In

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exploratory work, such as ours, it is often undesirable to obtain a false negative result, thereby prematurely rejecting a useful intervention [5]. Thus, we did not adjust for multiple comparisons, as mentioned in both our methods and limitations sections [4]. That said, in a definitive phase III trial, we firmly endorse a priori selection of a primary outcome, a statistical threshold, and a sample size. Vallance and Bolam rightfully suggest reporting effect sizes of exercise vs. control; they are 0.11 for numbness/tingling and 0.21 for hot/coldness in hands/feet.

Regarding the clinical significance of our observation that exercise can slightly attenuate CIPN symptom severity after 6 weeks of neurotoxic chemotherapy, we can examine change on the 0–10 patient-reported scales (0.42–0.46 units; Table 2 of [4]), effect sizes (0.11–0.21; reported herein), or number needed to treat using the dichotomous score (9.4–27.9; reported herein). In all cases, the magnitude of the protective effects of exercise on CIPN symptoms is relatively small [6]. However, CIPN is a cumulative toxicity that typically worsens over the weeks of chemotherapy, for example as illustrated by steady increases in severity of numbness and tingling over 12 weeks of paclitaxel (Fig. 4 from [7]). Thus, if our observed trajectory continues, then the cumulative benefits of exercise would be even greater than observed in our 6-week study. This is an empirical question for future studies that use interventions and assessments for more than 6 weeks.

Scientifically, we believe our results are significant in the broader study of CIPN and its treatment, given the dearth of promising treatment options for CIPN [8], and the lack of definitive phase III clinical trials testing the effects of exercise on CIPN where CIPN is the primary outcome. We believe this while still acknowledging that (1) our results should be interpreted with caution—as should results from *all* exploratory secondary analyses, (2) our observed effect sizes were relatively small, and (3) our observed CIPN symptom severity was relatively low. Clearly, our work makes way for additional high-quality research where CIPN is the primary outcome and where CIPN can be studied more rigorously, per a recent review of CIPN trials [9].

Taken together, there are many reasons to be excited about the use of exercise during chemotherapy in the prevention of CIPN as part of both supervised and self-management interventions [1]. Exercise has relatively little risk, it can be conducted in conjunction with other therapies, and it is also beneficial for attenuating other chemotherapy-induced toxicities such as fatigue, sleep disturbances, cognitive deficits, and distress [10]. We agree wholeheartedly with the commenting authors that we need more high-quality research on the effects of exercise on CIPN, and we hope to contribute to that research in the future. Indeed, we are currently working on two clinical trials to this end. We are also interested in multi-site clinical trials of CIPN, and we invite further collaboration, as previously suggested [1, 3].

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Compliance with ethical standards

Conflict of interest Several authors (I.R.K., C.K., M.C.J, and K.M.M.) received funding from the National Cancer Institute to support this work. J.S.G. received funding from Mundipharma and Regenacy Pharmaceuticals for other work (i.e., not this manuscript). The authors have full control of all primary data and agree to allow the journal to review the data if requested.

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