Exercise protocols: The gap between preclinical and clinical exercise oncology studies

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ARTICLE INFO

Keywords:
Preclinical
Clinical
Exercise Oncology
Translational failure
Gap analysis
Exercise protocols
Cancer-induced complications

ABSTRACT

Introduction: Preclinical studies provide foundational knowledge to develop new effective treatments for use in clinical practice. Similar to clinical exercise oncology studies, it is also important to monitor, identify and/or avoid cancer-induced complications in preclinical (e.g., murine) exercise oncology studies. This may help close the gap between preclinical and clinical exercise oncology studies. The aim of the present mini review is to provide insight into exercise protocol design in preclinical exercise oncology studies in order to close the preclinical-clinical gap. A secondary aim was to examine exercise-responsive outcomes in the preclinical versus clinical setting.

Method: We reviewed animal studies in exercise oncology. A literature search was performed in PubMed/Medline and studies in English were screened.

Results: We found that the majority of preclinical exercise protocols have not been at least tested clinically. We found some evidence that certain outcomes of preclinical studies (e.g., markers of cellular and molecular adaptation) translate to clinical studies. However, this translation was dependent on the use, by investigators in their study design, of suitable and applicable preclinical exercise protocols.

Conclusions: Cancer and its treatment-induced complications (e.g., fatigue, cardiac atrophy, cachexia, etc.) have largely been ignored in the exercise protocols of preclinical oncology studies. Preclinical exercise oncology studies should consider the limitations of human exercise oncology studies when conducting gap analysis for their study design to increase the probability that findings related to mechanistic adaptations in exercise oncology will be translatable to the clinical setting. By virtue of paying heed to patient compliance and adverse effects, clinical exercise oncology research teams must design relevant, feasible exercise protocols; researchers in preclinical exercise oncology should also take such factors into consideration in order to help bridge the gap between preclinical and clinical studies in exercise oncology.

1. Context

1.1. Translating protocols from preclinical to clinical studies

Gap analysis is a process that identifies what aspects of human study need to be supported by future preclinical studies. This process may also include defining the preclinical strategy that will address the requirements of the target regulatory body. In reviewing available information, literature should be evaluated not only for ‘content’ to support the preclinical strategy but also scrutinized for factors/issues that may render the findings not applicable to the investigator’s goals (e.g., technical or procedural issues) [1]. (This has parallels to conducting a systematic review—identifying risks of bias as well as the standardized overall effect size).

Though gap analysis is time consuming, thanks to the harmonization of different regulatory bodies [1], subsequent preclinical studies could be conducted at multiple locations (e.g., outsourcing globally) to expedite time lines and minimize costs. It is well known that the rate of
translating preclinical success into viable clinical applications is very low (~5%), due to many factors including poor experimental design, animal models and poor reporting owing to having not been tested in an practical manner [2]. Whereas various mitigation strategies are ongoing [3], the gap between preclinical and clinical utility shows little sign of closing [4]. Similar to investigational new drug development, translating preclinical exercise oncology findings to the clinical setting presents many challenges; for example, translating exercise protocols from the human to the animal and vice versa [5,6]. In this mini-review, we aim to highlight gaps between human and animal studies in exercise oncology, and discuss the exercise protocol framework to improve the translation rate between preclinical and clinical studies. We examine preclinical exercise protocols, their translation to clinical studies, and if/how clinical studies take into account preclinical exercise training frameworks. Lastly, we discuss the importance of developing an ‘optimal’ exercise training framework for preclinical exercise oncology in order to improve translation success into the clinical exercise oncology setting.

1.2. Mechanisms in exercise adaptation: considering limitations of human studies in preclinical studies

Exercise training has a myriad of pleiotropic effects on numerous cells, tissues, and organs of the body in both healthy as well as diseased states [2,7]. Exercise adaptations are underpinned by numerous signaling pathways as well as local and distant feedback loops that give rise to a new homeostatic state. The end result is an increase in cellular, tissue and organ fitness leading to wide-ranging disease improvements and decreases in health problems [8–13]. Therefore, there is considerable potential value in being able to appropriately apply preclinical exercise to disease states such as cancer. This includes developing relevant preclinical exercise models and protocols, including accounting for genetic factors [14–16], as well as mode, intensity, and duration, respectively. Combined, these factors will influence molecular and cellular adaptation [8–11,17], despite the presence of disease [10,13]. Despite its relatively low adoption in modern healthcare, exercise training ‘prescription’ offers considerable therapeutic potential [10,12,13] given that exercise training has direct impacts – from modifying cell function to inter-tissue crosstalk [12] – in chronic diseases including cancer [13,18]. Indeed, it is probably valuable to consider exercise prescription from two ‘lenses’—considering both clinical benefit as well as understanding prescription/adaptation at a molecular level [8,10,13].

Little data exists regarding how modifying exercise protocol parameters modifies the mechanisms that influence cancer survival, both preclinically and clinically. To evaluate whether the results of preclinical exercise oncology findings translate to clinical exercise oncology, protocols in preclinical study should be designed based on the framework of protocols considering the limitations of clinical studies.

Human and animal exercise activate a myriad of cellular pathways which contribute to remodeling and/or adaptation [8–11,13]; however, the extent to which given pathways yields anticancer benefits, and whether this is of the similar significance in animal and humans, is unclear. Nevertheless there is evidence of preclinical-clinical commonalities; for example, high intensity interval training appears to evoke similar potent benefits [19–23]. Understanding the exercise tolerance thresholds (especially clinically) together with exercise stimulus thresholds (to elicit a meaningful beneficial physiological response) will combine to establish suitable exercise protocols oncology studies. Further, expected adaptations (e.g., derived from healthy populations) need to be examined with actual adaptations that occur in the cancer/cancer therapy environment, taking into account both the altered biological (e.g., inflammatory) and physical (e.g., altered locomotor activity) environments.

1.3. Cancer and treatment-related fatigue: ignored factors in preclinical exercise protocol design

Fatigue is one of the main pervasive side effects of cancer [24–26]. It is also among the most common and challenging symptom during and after treatment [24,26–28]. The mechanistic pathways of cancer-induced fatigue in human and animals are poorly understood but include bio-behavioral factors (e.g., mood, depression, stress and sleep disturbance) [29–32], hypothalamic-pituitary-adrenal axis [29,30,32], neuroinflammation [33–35] and muscle wasting [30,32,36]. Several studies demonstrate that cancer [22,29,36] and its chemotherapy treatment lead to reduced voluntary wheel running activity of mice [25,37–41] or running speed reduced by 20% at the target intensity [42]. Cancer-induced skeletal muscle dysfunction [43,44] and cardiac atrophy [44] reduce locomotor activity and exercise capacity. Collectively, the debilitating complications of cancer – direct and indirect – are important to consider when designing preclinical exercise oncology studies. Results derived from preclinical studies that impose excessive pressure on animals to perform exercise training – often more than their voluntary capacity – can yield misleading interpretations and expectations of translation to the human condition [6]. Whereas exercise parameters in the clinical setting are likely to be of a milder intensity and geared toward doing no harm (in line with patient’s self-selected/voluntary effort), there is growing evidence (a recent systematic review identified 12 studies [45], all within the past decade) of efficacy/feasibility of high intensity training [46–48].

1.4. Exercise intensity in preclinical exercise oncology studies

VO\textsubscript{2peak} measurement not only is reported as the gold standard assessment of exercise capacity in patients, but is a strong independent predictor of the cancer patients mortality [49]. In a preclinical setting, serial measurements of VO\textsubscript{2max} are suggested to regulate running speed/exercise intensity [43]. Whereas running pace can be used as an indirect measure of oxidative capacity measuring VO\textsubscript{2peak} in rodents provides a more informative/standardizable readout of exercise intensity for exercise interventions as well as cancer-induced changes in locomotor activity in rodents. Indeed, a remarkable decline in indirect VO\textsubscript{2max}, running speed [42], and endurance exercise capacity [50] of rats with cancer throughout the study period revealed that cancer-bearing animals do not reach maximal VO\textsubscript{2max} compared to healthy controls. Based on these results [42,43,50], applying valid and reliable experimental models is essential to examine – and standardize across labs – the impact on cellular and molecular mechanism of exercise training for prevention, treatment and rehabilitation of chronic diseases [43].

In addition to improving understanding of mechanisms, the ability to standardize exercise protocols (e.g., based on VO2) will advance our understanding of the impact of cancer-, chemo- and hormone-therapy on function and fatigue. Although exercise training is a safe therapy to mitigate cancer-related fatigue and improve exercise tolerance in cancer survivors [51,52], and in mice [53,54], it is essential to consider the capacity of exercise tolerance and locomotor activity. Increased running speed/intensity during a preclinical exercise oncology study without considering exercise capacity may overlook cancer effects and treatment-induced side effects such as fatigue and reduced locomotor activity.

A method to assess fatigue in the rodent is locomotor activity reduction [29]. Recently, Dougherty JP et al. used a treadmill test to determine fatigue-like behavior in mice undergoing chemotherapy [55]. Although this method needs to be verified by future studies, it may be a good method to determine the side effect of cancer-, chemo- or hormone therapy in preclinical exercise intervention studies. Additionally, we have used [19] a method to design a suitable preclinical exercise protocol based on Leandro CG et al. [56] and Hoydal MA et al. [43]. We measured VO\textsubscript{2peak} of breast cancer-bearing mice indirectly prior to
starting the study. To assess the indirect VO_{peak}, mice started running on the motorized treadmill at a speed of 6 m min^{-1}. The speed was increased by 2 m min^{-1} every 3 min until the mice were unable to run and to maintain running speed on the treadmill. We kept this method weekly for 5 weeks (once every 6 days), and then every other week for 5 weeks (once every twelve days) by the end of the study. Indirect VO_{peak} measurement was performed in interventional groups, followed by 2 days rest to monitor any potential changes in mice running ability resulting from cancer (and/or adaptation to exercise), and also to select exercise intensity for the subsequent week. During our study [19], we observed that running ability and exercise tolerance of breast cancer bearing mice were significantly reduced after the second week of tumor palpation. Further, we found that running capacity of cancer bearing mice was progressively reduced, week by week, to the end of the study [19].

This Other preclinical studies have used a similar VO_{peak}-based frameworks [20–23]. Similar protocols were also used in diabetic [57, 58] and also fatty liver animals [12], aiming to generate information with a higher probability of translation to clinical studies. Using a progressive exercise protocol, or a protocol with a stable intensity during preclinical exercise oncology studies without estimating exercise capacity before and throughout the study may lower the translation rate, and widen and deepen the gap with clinical practice. Increasing running speed progressively [59, 60] or stabilizing speed and intensity during the study [61–68] may not take into account cancer-related complications and/or cancer therapeutic treatment-induced fatigue, potential cardiac atrophy and skeletal muscle dysfunction. Hence, preclinical exercise oncology studies should consider the intervention framework approaches based on the feasibility and suitability in clinical exercise oncology studies. Taken together, preclinical studies that have voluntary wheel running or exercise protocols designed based on VO_{peak} may have a better chance of successfully translated to clinical studies. Kumar 2011 has said “preclinical information is used to estimate an initial safe starting dose and dosing regimen for human trials” [1]. Thus, the analogue for exercise oncology, the exercise protocol, requires similar careful monitoring and ‘dosing’ in order to better translate preclinical findings.

1.5. Summary and future directions

Preclinical exercise oncology studies provide essential supporting scientific insight for clinical oncology trials. Nevertheless, a large number of preclinical exercise protocols have not been translated in clinical practice due to poor methodology and lack of the framework validation of protocols. Accordingly, we recommend, as a direction for future study, to researchers use a well-defined exercise protocol (including reporting speed, slope and VO_{peak}) prior to and during the study, such as those described by Hoydal et al. [43], Dougherty JP et al. [55] and Delphan et al. [19]. However, future research is needed to measure VO_{peak} directly in cancer bearing animal (e.g. mice and rats). Voluntary wheel running protocols are also viable exercise framework that may better account for the fatiguing aspects of cancer/therapy [22]. In this way, the effects of cancer/therapy on exercise tolerance and locomotor activity in cancer bearing animals can be standardized and the impact on mechanistic pathways quantified more reproducibly toward the ultimate goal of clinical translation. Researchers who have a good understanding of exercise protocol development in healthy and disease states, and in preclinical and clinical settings, will be best positioned to translate the potentially beneficial preclinical exercise-based effects to the clinical setting and, ultimately, cancer patient populations more broadly.

CRediT authorship contribution statement

Mahmoud Delphan: conceptualized the manuscript. Neda Delfan: reviewed literature contributed to the intellectual discussion, and revised the manuscript. Daniel West: reviewed literature contributed to the intellectual discussion, and revised the manuscript. Maryam Delphan: reviewed literature contributed to the intellectual discussion, and revised the manuscript.

Declaration of competing interest

The authors declare no conflict of interest.

References

[1] Kumar M, Longstreth J. Risks and Benefits of Conducting Preclinical Studies in the Global Setting. 2011.
[2] Lalu MM, Montroy J, Begley CG, Bubela T, Henniford V, Ripsam D, et al. Identifying and understanding factors that affect the translation of therapies from the laboratory to patients: a study protocol. F1000Research 2020;9:485.
[3] Hingorani AD, Kuan V, Finn C, Kruger FA, Gaulton A, Chopade S, et al. Improving the odds of drug development success through human genomics: modelling study. Sci. Rep. 2019;9(1):1–25.
[4] Seyhan AA. Lost in translation: the valley of death across preclinical and clinical divide. identification of problems and overcoming obstacles. Trans. Med. Comm. vol. 2019;4(1):1–19.
[5] Jones LW. Precision oncology framework for investigation of exercise as treatment for cancer. J Clin Oncol 2015;33(35):4134–7.
[6] Mello L, Hagar A. How to train a mouse-methodological issues in pre-clinical exercise oncology. Am. J. Cancer Res. 2019;9(6):1246.
[7] Wang R, Tian H, Guo D, Tian Q, Yao T, Kong X, et al. Impacts of exercise intervention on various diseases in rats. J. Sport Health Sci. 2020;9(3):21–27.
[8] Coffey VG, Hawley JA. The molecular bases of training adaptation. Sports Med 2007;37(9):737–63.
[9] Gibala MJ, Little JP, Macdonald MJ, Hawley JA. Physiological adaptations to low-volume, high-intensity interval training in health and disease. J Physiol 2012;590(5):1077–84.
[10] Egan B, Zierath JR. Exercise metabolism and the molecular regulation of skeletal muscle adaptation. Cell Metab 2013;17(2):162–84.
[11] Hawley JA, Hargreaves M, Joyner MJ, Zierath JR. Integrative biology of exercise. Cell 2014;159(4):738–49.
[12] Delfan M, Delfan N, West D, Nikpour H, Rostamkanhi H. High intensity interval exercise alters muscle IL-1β, FNDC5, and hepatic MMPs in animal model of ectopic expression of skeletal muscle—liver crosstalk. J Exercise Organ Cross Talk 2021;13(10):10–8.
[13] Hojman P, Gehl J, Christensen JF, Pedersen BK. Molecular mechanisms linking exercise to cancer prevention and treatment. Cell Metabolism 2018;27(1):10–21.
[14] West DW, Doering TM, Thompson JLM, Budlono BP, Lensard SJ, Koch LG, et al. Low responders to endurance training exhibit impaired hypertrophy and divergent biological process responses in rat skeletal muscle. Experim. Physiol. 2021;106(3):714–25.
[15] Lensard SJ, Rivas DA, Alves-Wagner AB, Hirshman MF, Gallagher LI, Constantin-Teodosiu D, et al. Resistance to aerobic exercise training causes metabolic dysfunction and reveals novel exercise-regulated signaling networks. Diabetes 2011;60(8):2717–27.
[16] Thompson IU, Jones LW, Koch LG, Britton SL, Neil ES, McGinley JN. Inherent aerobic capacity-dependent differences in breast carcinogenesis. Carcinogenesis 2017;38(9):920–8.
[17] Macnissi MJ, Gibala MJ. Physiological adaptations to interval training and the role of exercise intensity. J. Physiol. 2017;595(9):2915–35.
[18] Moore SC, Lee I-M, Weiderpass E, Campbell PT, Sampson JN, Kitahara CM, et al. Association of leisure-time physical activity with risk of 26 types of cancer in 1.44 million adults. JAMA Internal Medicine 2016;176(6):816–25.
[19] Delphan M, Agha Alinejad H, Delfan M, Dehghan S. Intratumoral effects of continuous endurance training and high intensity interval training on genes expression of miR-21 and bcl-2 in breast cancer bearing female mice. Iran J Breast Dis 2017;10(2):49–57.
[20] Delfan M, Raselkh Nejad Z, Delphan M. Synergistic effect of endurance training combined with curcumin on intratumoral expression of interleukin-4 (IL-4) and stat-6 in female mice with breast cancer. J Italian Journal of breast diseases. Iran J Breast Dis 2020;13(3):52–61.
[21] Ahmadabadi F, Sajpehbooj M, Huang C-J, Saffari I, Zardast M. The effects of high-intensity interval training and saffron aqueous extract supplementation on alterations of body weight and apoptotic indices in skeletal muscle of 4T1 breast cancer-bearing mice with cachexia. Appl. Physiol. Nutri. Metab. 2020;45(5):555–63.
[22] Fix DK, Counts BR, Smuder AJ, Sarzynski MA, Koh HJ, Carson JA. Wheel running improves fasting-induced AMPK signaling in skeletal muscle from tumor-bearing mice. Physiol. Rep. 2021;9(1):e14924.
[23] Ahmadabadi F, Sajpehbooj M, Hedayati M, Hoshyar R, Huang C-J. Treatment-induced tumor cell apoptosis following high-intensity interval training and saffron aqueous extract in mice with breast cancer. Physiol. Intern. 2021;108(1):19–26.
[24] Aoyagi W, Naito Y, Takagi T, Tanimura Y, Takamari Y, Kawai Y, et al. A novel myokine, secreted protein acidic and rich in cysteine (SPARC), suppresses colon tumorigenesis via regular exercise. Gut 2013;62(6):882–9.
[25] Vichaya EG, Mölkeniemi JM, Vermeer DW, Walker AK, Feng R, Holder G, et al. Sickness behavior induced by cisplatin chemotherapy and radiotherapy in a murine
head and neck cancer model is associated with altered mitochondrial gene expression. Behav Brain Res 2016;297:241–50.
26. Tasch H, Wolff BJ, Wolff JE. Fatigue in Cancer Treatment Studies: analysis of Placebo Arms. Anticancer Res. 2022;42(1):45–52.
27. Zomeck JA, Fey EG, Lyng GD, Sonsti ST. A clinically translatable mouse model for chemotherapy-related fatigue. Comp Med 2013;63(6):491–7.
28. Montimer JE, Barsewicz AM, Bennett CL, Berger AM, Cleland C, DeVader SR, et al. Studying cancer-related fatigue: report of the NCCN scientific research committee. J Natl Compr Canc Netw 2010;8(12):1351–9.
29. Bower JE, Lamkin DM. Inflammation and cancer-related fatigue: mechanisms, contributing factors, and treatment implications. Brain Behav Immun 2013;30:548–57.
30. Xu J-Y, Fan V-H, Geng J-Z, Chen X-H, Qi Z-J, Li X-J. Mechanism of Cancer-Induced Fatigue/TMBMCancer 2021;4(3):12.
31. Bower JE. The role of neuro-immune interactions in cancer-related fatigue: Biobehavioral risk factors and mechanisms. Cancer 2019;125(3):353–64.
32. Yang S, Chu S, Gao Y, Ai P, Liu Y, Li X, et al. A narrative review of cancer-related fatigue (CRF) and its possible pathogenesis. Cells 2019;8(7):726.
33. Norden DM, Bicer S, Clark Y, Jing R, Henry CJ, Wold LE, et al. Tumor growth increases neuroinflammation, fatigue and depressive-like behavior prior to alterations in muscle function. Brain, Behavior, Immunity 2015;43:76–85.
34. Weymann KB, Wood L, Zhu X, Marks DL. A role for orexin in cytotoxic chemotherapy-induced fatigue. Brain, Behavior, and Immunity 2014;37:84–94.
35. Mcleary F, Davis A, Rudrawar S, Perkins A, Anoopkumar-duke S. Mechanisms underlying select chemotherapeutic-agent induced neuroinflammation and subsequent neurodegeneration. European J. Pharmacol. 2019;842:49–56.
36. Norden DM, Bicer S, Clark Y, Jing R, Henry CJ, Wold LE, et al. Tumor growth increases neuroinflammation, fatigue and depressive-like behavior prior to alterations in muscle function. Brain Behav Immun 2015;43:76–85.
37. Sandri M, Lin J, Handschin C, Yang W, Arany ZP, Lecker SH, et al. PGC-1alpha protects skeletal muscle from atrophy by suppressing FoxO3 action and atrophy-specific gene transcription. Proc Natl Acad Sci U S A 2006;103(44):16260–5.
38. Ray MA, Trammell RA, Verhulst S, Ran S, Toth LA. Development of a mouse model for assessing fatigue during chemotherapy. Comp Med 2011;61(2):119–30.
39. Mahoney SE, Davis JM, Murphy EA, McClellan JL, Gordon B, Pena MM. Effects of 5-fluorouracil chemotherapy on fatigue: role of MCP-1. Brain Behav Immun 2013;27(1):155–61.
40. al-Majid S, McCarthy DO. Cancer-induced fatigue and skeletal muscle wasting: the role of exercise. Biol Res Nurs 2001;2(3):186–97.
41. Weymann KB, Wood L, Zhu X, Marks DL. A role for orexin in cytotoxic chemotherapy-induced fatigue. Brain, behavior, and immunity 2014;37:84–94.
42. Alves CR, das Neves W, de Almeida NR, Eichelberger EJ, Janini PR, Voltairelli VA, et al. Exercise training reverses cancer-induced oxidative stress and decrease in muscle COP2S/TRIP15/ALIEN. Molecular Metabolism 2020;39:101012.
43. Hoiyad MA, Wiafol U, Kemi OJ, Ellingsen O. Running speed and maximal oxygen uptake in rats and mice: practical implications for exercise training. Eur. J. Prev. Cardiol. 2007;14(6):753–60.
44. Argiles JM, Busquets S, Stemmler B, Lopez-Soriano FJ. Cancer cachexia: understanding the molecular basis. Nat Rev Cancer 2014;14(11):754–62.
45. Maugele H, Freitag N, Wilhelmi J, Yang Y, Cheng S, Bloch W, et al. High-intensity interval training in the therapy and aftercare of cancer patients: a systematic review with meta-analysis. J. Cancer Surviv. 2019;13(2):205–23.
46. Smetni J, Lindner N, Reus-Boest M, Holmberg HC, Sperlachia B. A 3-week multimodal intervention involving high-intensity interval training in female cancer survivors: a randomized controlled trial. Physiol. Rep. 2016;4(3):e12693.
47. Macdonald G, Stitfinger A, Deal MA, Hanson ED, Ferraro S, Pieper CF, et al. A pilot study of high-intensity interval training in older adults with treatment naive chronic lymphocytic leukemia. Sci. Rep. 2021;11(1):1–14.
48. Hanson ED, Sheaff AK, Sood S, Mal F, Francis JD, Goldberg AP, et al. Strength training induces muscle hypertrophy and functional gains in black prostate cancer patients despite androgen deprivation therapy. Jbiomed. Med. Sci. 2013;68(4):490–8.
49. Betof AS, Dewhirst MW, Jones LW. Effects and potential mechanisms of exercise training on cancer progression: a translational perspective. Brain Behav Immun 2013;30:87S–87.