Precision Oncology Framework for Investigation of Exercise As Treatment for Cancer

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Introduction

In recent years, a new line of investigation has emerged that addresses the novel question of whether exercise has an impact on cancer outcomes. Advances in genomic profiling have increased our understanding of the molecular and genetic complexity of human cancer and, although many challenges remain,[1,2] several scenarios suggest that successfully matching a genomic alteration with drug therapies that target the alteration can result in striking durable responses.[2,3] Critical prerequisites underlying these successes include having an adequate understanding of the biologic mechanisms of the drug's action, identifying the biologically effective dose, and determining the predictors of response to guide patient selection. Arguably, elucidation of these prerequisites is required to optimize the efficacy of any therapeutic strategy,[4] including exercise treatment.

Almost a decade ago, the National Cancer Institute published a framework outlining a sequence of steps to facilitate the advancement of candidate lifestyle interventions, including exercise, from early discovery to definitive phase III trials in cancer control.[5] Unfortunately, research in exercise-oncology, in general, has not adhered to the National Cancer Institute's recommendations nor has it taken advantage of the recent developments in genomic medicine. This commentary presents a modified framework that uses a precision oncology approach to facilitate investigation of exercise as a candidate anticancer treatment (Table 1). Adoption of this framework seeks to change the longstanding rhetoric of "exercise works for everything" and the related approach of "one size fits all" generically dosed exercise to one in which exercise treatment is matched to the patient on the basis of the molecular profile of the tumor and the patient's genotype. Here, this approach is discussed by dividing it into the following seven steps: discovery, evaluation of causality (epidemiology), molecular epidemiology, preclinical testing, safety and tolerability clinical trials, early signal-seeking/biomarker-driven clinical trials, and definitive clinical trials.

Discovery

The use of well-designed epidemiologic studies that investigate the correlation between postdiagnosis exercise and cancer outcomes (eg, recurrence, tumor biology) is an essential step in the translational continuum.[6] In the first published study, Holmes et al[7] found that ≥ 9 metabolic equivalent tasks (METs; ratio of metabolic rate [and therefore the rate of energy consumption] during a specific physical activity to a reference metabolic rate, set by convention to 3.5 mL O_2/kg/min of exercise [equivalent to brisk walking for 150 min/wk]) was associ-ated with an adjusted 50% relative risk reduction in breast cancer mortality compared with less than 3 METs (equivalent to brisk walking for < 60 min/wk) in women with early-stage disease. First reports of an inverse relationship between exercise and risk of recurrence and death as a result of colorectal and prostate cancer followed shortly thereafter.[8-10]

Evaluation of Causality

This step involves evaluating the consensus of observational findings on the basis of the Bradford-Hill criteria (Table 1).[11] Unfortunately, only a few studies have been published that examined the relationship between postdiagnosis exercise and cancer-specific outcomes; thus, establishing whether a consensus of evidence exists in any disease site is premature at present. The majority of evidence exists in early-stage breast cancer, for which approximately eight studies have examined that relationship.[12,13] An initial evaluation of this evidence suggests that many of the Bradford-Hill criteria are not achieved (Table 1); thus, there is currently insufficient evidence to support the statement that postdiagnosis exercise improves cancer-specific outcomes. Irrespective of the available evidence base, observational data alone are insufficient to support definitive phase III trials.[5] Indeed, the limitations of launching definitive trials on the basis of observational data have been illustrated in cancer micronutrition research.[14-16] Clearly, there is a significant risk for the development of exercise as a candidate anticancer therapy to follow a development path similar to that of micronutrition research. However, the adolescent nature of the research on exercise and cancer outcomes provides a unique but finite opportunity to rigorously develop and test exercise so as not to make the mistakes of the past.

Molecular Epidemiology

The majority of investigations of the impact of exercise on cancer outcomes have assumed that cancer is a genetic and physiologically homogeneous disease.[17] However, the impact of exercise may differ as a function of clinicopathologic features (eg, tumor size, estrogen receptor status) in early-stage breast cancer (Jones LW, manuscript submitted for publication),[12] whereas in colorectal cancer, tumor *PTGS2* positivity, CTNNB1 negativity, and expression of CDKN1B (p27) predict sensitivity to exercise.[18-20] Clearly, these hypothesis-generating findings require validation in an independent cohort, together with confirmation in appropriate preclinical models to be considered useful for informing patient selection into exercise trials. There are, however, significant scientific as well as logistical challenges

Table 1. A Precision Oncology Framework for Investigating Exercise Treatment

Translational Development Pathway Step	Description	Example
Discovery	Initial discovery of a correlation between the exposure and the clinical disease end point of interest (ie, cancer-specific outcomes such as recurrence events, time to progression, cancer-specific mortality).	Higher exposure to (self-reported) postdiagnosis exercise is associated with a reduced risk of recurrence and cancer death in non–small-cell lung cancer.
Evaluation of causality	Consensus of epidemiologic data showing a consistent relationship between exposure to treatment and the clinical disease end point of interest meeting the Bradford-Hill criteria (eg, an association is more likely to be causal when it is temporally related, that is, the likely cause precedes the effect; it is reasonably strong within cohorts and across study designs; a dose-response relationship exists; the observed relationship is biologically plausible; it is unlikely to be explained by alternative associations; and cause and effect can be established via experimental research.	Higher exposure to (self-reported) postdiagnosis exercise is consistently associated with a reduced risk of recurrence and cancer death in non–small-cell lung cancer in a dose-dependent manner, after adjustment for important clinical covariates and treatment.
Molecular epidemiology/ molecular screening platforms	Application of -omic-based platforms to elucidate whether certain patient subtypes are more responsive to the exposure than others. This information can be used to guide patient selection.	Higher exposure to (self-reported) postdiagnosis exercise is associated with a reduced incidence of recurrence and cancer death in non–small-cell lung cancer (in a dose-dependent manner), but such associations appear to be confined to tumors expressing a certain molecular marker (eg, HER1/EGFR overexpressing tumors).
Preclinical testing	Consensus of data showing that the treatment exposure causes inhibition and/or modulation of tumor end points in relevant animal models.	Forced treadmill running is associated with inhibition of tumor growth in a genetically engineered mouse model or patient-derived xenograft of HER1/EGFR overexpressing non–small-cell lung cancer; a biologically effective dose has been identified, as well as predictors of response.
Safety and tolerability clinical trials	Initial first-in-human studies demonstrating the safety and tolerability of the planned exercise treatment dose in the target population and setting of interest. Preliminary information on treatment efficacy should also be obtained.	Supervised aerobic training consisting of five walking sessions per week at 55% to 80% of exercise capacity for 30 to 60 minutes per session for 16 weeks is safe (no adverse events) and tolerable (adherence rates > 70%) and is associated with improvements in exercise capacity in HER1/EGFR overexpressing non–small-cell lung cancer.
Signal-seeking/ biomarker-driven clinical trials	Preliminary single-arm or randomized phase II trials to investigate initial clinical activity (eg, modulation of the pathway/molecular target of interest, identification of predictors of response) of the treatment in the target oncology population and setting of interest to inform a go/ no-go decision on whether to further pursue the line of investigation.	Supervised aerobic training consisting of five walking sessions per week at 55% to 80% of exercise capacity for 30 to 60 minutes per session for 16 weeks is associated with a favorable improvement in clinical response rate with a numerical improvement in progression-free survival compared with usual care. A somatic mutation in the HER1/EGFR tyrosine kinase domain correlated with response to exercise treatment.
Definitive clinical trials	Large-scale, definitive, randomized controlled phase III trials adequately powered to detect clinically important differences on accepted clinical end points (eg, progression-free survival, overall survival) in the target setting.	Supervised aerobic training consisting of five walking sessions per week at 55% to 80% of exercise capacity for 30 to 60 minutes per session for 16 weeks improves progression-free survival and overall survival in HER1/ EGFR overexpressing non–small-cell lung cancer.

Abbreviation: HER1/EGFR, human epidermal growth factor receptor 1/epidermal growth factor receptor.

to conducting genomically informed early clinical trials, as discussed elsewhere.[1,21,22]

Preclinical Testing

Preclinical testing is a major facet in the development of all anticancer agents and treatments.[23] Several in vitro and in vivo model systems are currently available to oncology researchers. For instance, within mouse models (the most widely used for in vivo oncology studies), several different systems are available, including cell line xenografts, patient-derived xenografts (PDXs), syngeneic allografts, and genetically engineered mouse models. The advantages and disadvantages of each model have been reviewed elsewhere.[23,24] Other model systems that include zebrafish and *Drosophila* offer unique insights complementary to those provided by rodent model systems.[25,26] Because there is a paucity of work investigating the antitumor effects of exercise on tumor progression or metastasis in

preclinical models in any oncology scenario and because the available evidence base is characterized by significant methodologic heterogeneity, there are currently insufficient data to confirm or refute the biologic plausibility of the antitumor effects of exercise.[27]

With a view toward future research priorities, no one model will fit all exercise discovery questions. Model selection should be based on attempting to match the expected mechanism of action (of exercise) with the biology of the target or on model systems that express or are dependent on the target. Such selection can be further guided by findings from observational studies. Another important consideration somewhat unique to preclinical exercise discovery efforts is how exercise doses in preclinical model systems can be extrapolated to equivalent doses in humans. In drug development, the starting dose of new agents in first-in-human phase I studies is usually one-tenth of the maximum-tolerated dose or dose-limiting toxicity in rodents; interspecies (animal to human) scaling factors are then applied to

normalize to body-surface area and dosage in milligrams per kilogram.[28,29] Of course, such metrics do not apply to exercise treatment, but elucidation of standardized metrics that can be used to inform exercise doses in humans would represent a major advance in the field. In this commentary, preclinical testing and initial clinical studies are presented as sequential steps, but investigators are encouraged to evaluate exercise treatment efficacy across model systems. For instance, a synchronous co-clinical trial (ie, mouse studies in conjunction with a parallel human trial) is one such approach. In these designs, preclinical studies can be used to anticipate the results of the human study and to inform analysis of the human data. For example, a co-clinical trial design could be adopted to examine the patient-derived effects of exercise treatment in PDXs implanted into mice. Concurrently, the corresponding patient could also be treated with the equivalent dose of exercise to assess similar patient-derived markers. Such a design would permit comparison of whether exercise-related changes in the PDX are recapitulated in the patient, providing validation of the PDX model for future exercise discovery efforts.

Safety and Tolerability of Clinical Trials

Traditional phase I parameters used to evaluate the safety and tolerability of a new anticancer approach generally do not apply to the investigation of exercise. The prevailing dogma is that exercise is not a drug, but rather it is a nontoxic strategy that exhibits a markedly different safety profile than conventional or novel anticancer agents. Although exercise is not a drug, it does confer drug-like effects that cause significant perturbation to host homeostasis.[30] In addition, patients with cancer are typically older, and a significant proportion of them present with concomitant comorbid conditions that are further compounded by the direct and indirect effects of anticancer therapy.[31,32] Consequently, patients with cancer may be at heightened risk of an exercise-related event.[33] Thus, a prerequisite for initiating clinical exercise trials that have the primary objective of evaluating effects on tumor biology and/or cancer outcomes is confirmation that the planned exercise dose is safe and tolerable in the target patient population. Tolerability can be evaluated by study attrition, exercise compliance, and frequency of dose modification, whereas safety can be evaluated by the type and prevalence of serious and nonserious adverse events during exercise-based assessments and exercise training sessions. The standardized and widely adopted Common Terminology Criteria for Adverse Events is applicable to all oncology clinical trials, regardless of chronicity or modality and is thus appropriate for adoption in exercise trials. The threshold of acceptable tolerability and safety needs to be defined a priori (eg, a study attrition rate of $\leq 20\%$, an exercise compliance rate $\geq 70\%$, or a specific threshold of adverse events.

In drug trials, evidence that the compound possesses pharmacokinetic and pharmacodynamic (PD) activity is another standard prerequisite.[34] Traditional markers of pharmacokinetic activity are of limited value in evaluating exercise treatment; however, certain PD tumor markers may be appropriate (eg, the effects of exercise on established surrogates of antitumor efficacy and/or activity such as modulation of the estrogen receptor pathway in estrogen receptor–positive breast cancer). It is also essential to establish fidelity of the tested exercise dose; for instance, investigators can use established end points such as exercise capacity (for aerobic training interventions), although the physiologic and biologic effects of exercise vary dramatically depending on the nature of the prescription.[35] In other words, an exercise dose demonstrated to improve exercise capacity may be distinct from the dose required to modulate PD tumor markers.[36] The fundamental principles of prescribing exercise in exercise-oncology have been reviewed previously.[35]

Early Signal-Seeking/Biomarker-Driven Clinical Trials

This step is designed to evaluate whether exercise treatment modulates the tumor pathway or target of interest and identifies predictors of response; such trials also explore whether there is a signal for clinical efficacy or benefit. These early studies can inform a go/no-go decision on whether to advance exercise treatment on to definitive testing. By definition, early signal-seeking trials require re-evaluation of tumor characteristics via biopsy (of accessible tissue if in the metastatic setting), which can pose significant challenges. Rapid advancements in liquid biopsy discovery efforts will potentially permit evaluation of tumor response via assessment of circulating tumor cells, circulating tumor DNA, exosomes, and secretomes,[37] which will greatly facilitate the investigation of exercise as a candidate anticancer treatment. Patient selection in these trials should be guided by a priori validated predictors of response (so-called basket trials). Alternatively, the activity of exercise could be studied in an unselected population followed by genomic profiling to identify predictors of response that would inform subsequent prospective screening.[38]

Definitive Clinical Trials

The final step is adequately powered definitive phase III testing. Conducting such trials represents a significant challenge in oncology, given the unique methodologic aspects inherent in exercise treatment trials (eg, specialized facilities, equipment, and personnel required to deliver and implement the intervention). Nevertheless, conducting such trials appears to be possible, with at least one currently underway. The Colon Health and Life-Long Exercise Change trial is an international, multicenter phase III trial investigating the effects of structured exercise treatment on recurrence and cancer-specific mortality in 962 patients with resected stage III colorectal cancer.[39] The feasibility of a large, multicenter definitive phase III exercise trial has also been demonstrated in stable patients with heart failure.[40,41]

Summary

Promising discovery (epidemiologic) data have led to the provocative hypothesis that exercise treatment may improve cancer outcomes, fueling calls for the need for large phase III trials to definitively test this question. Emerging epidemiologic data suggest that the potential efficacy of exercise differs on the basis of tumor subtype. The heterogeneity in response creates the strong hypothesis that a precision oncology approach is required to optimize the benefit and safety of exercise as a candidate antitumor strategy. This commentary has presented one potential translational framework that may facilitate these efforts. It is hoped that the concepts described here will provide the platform for constructive dialogue and interdisciplinary collaboration to optimize the therapeutic promise of exercise treatment.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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