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EDITORIAL COMMENT

Inclusion of Exercise in Cancer Treatment Planning

When Is the Right Time?*

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The prescription of exercise for patients with cancer is now clearly recommended by multiple national agencies and professional organizations, including the American Society of Clinical Oncology.[1,2] The basis of these recommendations is predominantly derived from studies that have demonstrated exercise-related improvements in patient-reported outcomes, treatment-associated adverse effects, cardiorespiratory fitness (CRF), and overall physical functioning.[3-6] Emerging preclinical findings and clinical observations additionally indicate an anticancer effect of exercise via mechanisms that directly inhibit tumor progression and/or synergize with standard cancer therapies.[7,8] Despite these benefits, multiple competing priorities have limited the implementation of exercise oncology practice guidelines in the United States.[9,10] The rapid advancement and availability of novel cancer therapeutics, with clinical benefit ranging from low to high impact, have ushered in a decision-making paradigm that requires highly nuanced conversations and planning between patients and their oncologists to develop a treatment approach that aligns with patient priorities while balancing clinical efficacy with toxicity—including physical, financial, and psychosocial (eg, access and time commitment). Within this context, the consideration of any treatment recommendation, including exercise, is scrutinized against competing priorities in order to design a high-yield treatment plan. Although exercise is a low-toxicity intervention, several questions surrounding its optimal use to maximize clinical yield have made it challenging to prescribe exercise as part of a cancer treatment plan, relegating exercise to the realm of "general recommendations" that are mentioned but often forgotten.

Recently updated guidelines from the American College of Sports Medicine now include exercise dosing information, which helps to provide specificity for the prescription of exercise in oncology.[2] However, key questions remain including: when do we prioritize exercise across the cancer treatment continuum, and should exercise dosing be modified as treatment milestones are accomplished and patient needs shift? Several randomized control trials have demonstrated that exercise after completion of cancer therapy improves various patient-reported outcomes and CRF.[3,4] Fewer studies have tested exercise during active cancer treatment (eg, chemotherapy) and have been challenged by suboptimal adherence/attendance rates.[11-14] Data supporting the superiority of exercise during active cancer treatment vs the post-treatment/survivorship setting are needed to compel patients and their oncologists to prioritize exercise earlier in the treatment course.

In this issue of *JACC: CardioOncology*, van der Schoot et al[15] report results from the ACT (Optimal Timing of Physical Activity in Cancer Treatment) trial, a randomized open-label trial testing a 24-week exercise intervention initiated during or after curative-intent chemotherapy in a study population predominantly comprising patients with breast, testicular, or colon cancer. Participants received

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standard chemotherapy regimens based on primary diagnosis, which ranged from 12 to 24 weeks. The study intervention was split between supervised exercise for the initial 12 weeks, followed by home-based exercise for the subsequent 12 weeks. At 1 year after the exercise intervention, there was no difference in CRF (quantified by peak oxygen uptake) between patients that started exercise during chemotherapy vs those that started after chemotherapy. Reduction in CRF was attenuated immediately postchemotherapy in the group that initiated exercise during chemotherapy. The exercise intervention improved several secondary outcomes in both groups, including quality of life, muscle strength, and fatigue.

This study provides several key insights that help address the question of when to prioritize exercise during cancer therapy. First, supervised exercise during chemotherapy was safe and tolerable, consistent with prior studies.[3,6] Second, supervised exercise during chemotherapy had early efficacy for mitigating chemotherapy-related decline in CRF. However, patients that initiated exercise after chemotherapy ultimately regained CRF and physical function to the same degree as those that started exercise during chemotherapy—a finding that is reassuring for patients unable to exercise during chemotherapy. Patients in both groups experienced improvements in fatigue, a clinically impactful finding given the lack of effective treatments for this highly prevalent and distressing adverse effect. Finally, exercise was efficacious in the setting of multimodality therapy, demonstrated by improvements in CRF in patients that received chest radiotherapy and chemotherapy.

Additional trials that build upon the findings of van der Schoot et al[15] are needed to further optimize exercise timing and duration in oncology practice. Among breast cancer patients randomized to start exercise during chemotherapy in the ACT trial, over 80% had already received 6 to 12 weeks of chemotherapy before starting exercise.[15] Furthermore, home-based exercise did not improve CRF after a period of supervised exercise. It is possible that initiation of exercise at the start of chemotherapy and/or longer-term supervised exercise may provide even greater protection of CRF. This hypothesis will be addressed by a recently completed phase 2 trial that randomized patients with breast cancer to receive usual care (control arm) or 1 of 3 exercise timelines: starting at the initiation of chemotherapy, after chemotherapy, or both during and after chemotherapy (Supervised Aerobic Training During or After Chemotherapy for Operable Breast Cancer; NCT01943695).

Adherence and tolerability are critical factors that can limit the feasibility, duration, and efficacy of exercise interventions. In the ACT trial, the dropout rate was 29%, and approximately one-third of patients did not log adherence during home-based exercise.[15] Additionally, CRF recovery in participants that started supervised exercise after completing chemotherapy caught up to participants that started exercise during chemotherapy but transitioned to home-based exercise after chemotherapy. These findings suggest the superiority of supervised exercise over home-based exercise, while highlighting the challenges of maintaining adherence. How do we reconcile the prescription of supervised exercise, which typically requires in-person attendance at an exercise facility, with limited adherence during active cancer treatment? To address this challenge, our group is testing novel digital approaches that enable at-home telemedicine delivery of supervised exercise with remote monitoring of physiological responses (eg, Exercise Treatment With Standard Therapy for Metastatic Breast Cancer, NCT03988595; Study of the Effects of Pre-surgical Aerobic Exercise on Patients With Solid Tumors, NCT03813615). Finally, adherence metrics beyond conventional lost to follow-up and attendance rates could provide additional information to guide exercise prescription. For example, relative dose intensity—a metric commonly applied to chemotherapy delivery—may be used to better characterize exercise dose delivery and dose response by accounting for exercise dose modifications, interruptions, or early termination of exercise sessions.[16] Dose delivery information would be helpful when counseling patients by providing benchmarks and expectations for exercise response.

Understanding how to prioritize exercise as part of cancer treatment is critical for clinical implementation, and the work of van der Schoot et al[15] provides a significant contribution by addressing when to prescribe exercise. Findings from the ACT trial help to inform the clinical application of exercise and

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underscore the need for further investigation of exercise dosing, timing, and individual response to equip clinicians with the data and knowledge that are required to prioritize exercise in cancer treatment planning.

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