

Challenges in enhancing physical performance in thoracic cancer cachexia

Cancer cachexia is a hypercatabolic state associated with malignant tumors and is frequently observed in newly diagnosed advanced lung cancer.¹ A clinically significant decline in physical performance is a serious consequence of cancer cachexia, especially in the elderly population²; however, no existing pharmacological or nonpharmacological interventions can mitigate or prevent this essential outcome.³ Multimodal interventions, which utilize the synergetic interaction of exercise and nutritional advice with optimal protein supplementation, were shown to enhance the physical performance of athletes and sarcopenic individuals.^{4,5} Thus, this combination has been suggested to have potential in the treatment of cancer cachexia.⁶ However, while the nutritional advice with oral nutritional supplements was somewhat standardized and shown to increase weight in cancer cachexia, evidence relating to its exercise counterpart is still lacking.⁷

The optimal combination of exercise and nutritional intervention has been tested in ongoing trials for patients at high risk for cachexia in advanced cancers. Solheim et al. reported the results of a multinational, randomized phase 2 study (Pre-MENAC study, feasibility study) of multimodal intervention in patients with advanced non-small-cell lung cancer (NSCLC) and pancreatic cancer.⁸ Their interventions consisted of nutritional counseling, aerobic and resistance training, celecoxib, and energy-dense supplements rich in eicosapentaenoic acid. Compliance for each intervention was 76% for celecoxib, 60% for exercise intervention, and 48% for oral nutritional supplements. However, the combination of two or three interventions achieved compliance of only 20–48% and 12%, respectively, suggesting a trade-off between the number of interventions and the level of compliance expected. Poor compliance may be due to the burden of multiple evaluations, additional effort, and time spent on the interventions. The efficacy of this intervention is currently being tested in a randomized controlled study (MENAC Study, Trial Registration No. NCT02330926), with bodyweight as the primary endpoint. Another non-pharmacological multimodal intervention for cancer cachexia was developed in Japan based on behavioral change techniques to improve patient tolerability and compliance. The Nutrition and Exercise Treatment for Advanced Cancer

(NEXTAC) program consists of nutritional counseling with supplements rich in branched-chain amino acids, home-based resistance training, and promotive counseling for physical activity.⁹ The NEXTAC program was designed to prevent disability in elderly patients at risk for cancer cachexia who had advanced NSCLC or pancreatic cancer and were scheduled to start systemic chemotherapy. A feasibility study (NEXTAC-ONE Study) reported excellent attendance (96.7%) and compliance with whole-program intervention ($\geq 90\%$). Additionally, $\geq 70\%$ of patients applied the insights from the health education and increased indoor or outdoor activity. The efficacy of the NEXTAC program is currently being tested in a randomized controlled study (NEXTAC-TWO Study, Trial Registration No. UMIN000028801), where disability-free survival is the primary endpoint.¹⁰

In January 2021, anamorelin hydrochloride, a selective ghrelin receptor agonist, was approved for marketing as the first specific medication for cancer cachexia in Japan; it has a strong orexigenic effect and increases lean body mass in cachectic patients with advanced NSCLC or gastrointestinal cancers.³ However, when used alone, anamorelin hydrochloride did not improve physical function, such as hand-grip strength or 6-min walking distance, in multiple randomized controlled trials. One possible reason may be a lack of contemporary nutritional and exercise interventions. Thus, this novel agent has the potential to provide an opportunity for the next generation of multimodal interventions, which combine pharmacological and nonpharmacological interventions in cancer cachexia.

Recently, a multicenter randomized controlled trial has launched in Japan, aiming to enhance physical performance in cancer cachexia by combining anamorelin hydrochloride with the NEXTAC program (NEXTAC-THREE Study, Trial Registration No. jRCTs041210053). The target population was elderly patients with newly diagnosed advanced NSCLC without driver oncogenes who have cancer cachexia and are scheduled to start first-line systemic chemotherapy. Approximately 40% of the target population may experience clinically meaningful worsening of walking capacity (defined as 40 m reduction in 6-min walking distance, or unable to be assessed) during the first 3 months.⁹ Researchers hypothesized that the investigational arm (anamorelin plus

NEXTAC) reduces the worsening ratio by 30% in the control group (anamorelin alone) with 80% statistical power (cohort 1, 2-arm randomized controlled study, $N = 60$). They also assessed the feasibility of the investigational arm for pancreatic cancer (cohort 2, single-arm, $N = 30$). If these multimodal programs are shown to be feasible and effective, they might be further tested to improve oncologic outcomes, health-related quality of life, or overall survival time in the subsequent phase 3 study.

The most meaningful endpoint of cancer cachexia care might be prolonging active life with satisfying quality of life.² However, increasing lean body mass, the standard endpoint in cachexia trials, may not always contribute to an ultimate endpoint, as shown in the anamorelin trials.³ In addition, each intervention component, including medication, exercise, or nutrition, is insufficient to improve physical function in cancer cachexia when used alone. Therefore, now is the time to attempt to enhance the physical performance of patients with cancer cachexia and seek an advance in the quality of their care using a tri-combination strategy.

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CONFLICT OF INTEREST STATEMENT

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