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COMMENTARY

Mirtazapine as an Appetite Stimulant in Patients With Non–Small Cell Lung Cancer

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Abstract

Cancer cachexia is a multifactorial paraneoplastic syndrome that almost universally affects cancer patients. Our current understanding of its physiopathology is incomplete, which hinders the development of effective treatments. As such, pharmacological agents are being evaluated, and non-pharmacological measures are employed to treat this condition. Here, we comment on the results of a phase II randomized trial of mirtazapine to evaluate its efficacy and toxicity. While the authors conclude that mirtazapine may improve nutritional status and represent an accessible and well-tolerated option, the results do not fully support the study's conclusions.

Introduction

Cancer cachexia is a multifactorial paraneoplastic syndrome commonly associated with advanced stages of cancer and is at least partly responsible for poor responses to cancer treatment and death. There is still an incomplete understanding of the metabolic dysregulation induced by a tumor that leads to the appearance and persistence of cachexia. To date, there are no therapies for successfully managing the cachectic patient. Current care measures for cachectic individuals are focused on nutritional supplementation, exercise, and pharmacological agents that include appetite stimulants such as megestrol acetate, ghrelin analogs, central nervous system drugs, anabolics, and anti-inflammatory drugs such as steroids and thalidomide, frequently in combination due to the multifactorial nature of the disease[1][2].

Main Text

A recently published randomized phase II clinical trial compared mirtazapine versus placebo in advanced Non-Small Cell Lung Cancer (NSCLC) diagnosed with cachexia[3]. A total of 86 patients were randomized, 43 to the placebo and 43 patients to mirtazapine. Treatment consisted of mirtazapine, 15 mg, or placebo for 2 weeks, followed by a dose escalation to 30 mg until week 8 or placebo. Both groups received nutritional assessment and dietary advice. Baseline

characteristics were similar between groups. Authors found that compared to placebo, mirtazapine statistically significantly increased energy intake and carbohydrates at 4 weeks, and fats at 8 weeks (Table 3). Nevertheless, the intergroup comparison showed no statistically significant differences between mirtazapine and placebo in 12 of the anthropometric, body composition, and appetite difference parameters evaluated at 4 and 8 weeks, except sarcopenia (Table 2). Authors reported that mirtazapine significantly decreased the proportion of patients with sarcopenia (82.8% vs 57.1%, p=0.03) at 8 weeks compared to placebo.

Clinically and biologically, the decrease in the proportion of sarcopenia-free patients 5 (17.2%) on placebo and 15 (42.9%) (which was not operationally defined) is hard to explain. It is known that nutritional supplementation alone does not prevent the loss of muscle mass or strength but indicates the need for supplements to be coupled with both resistance and endurance training in cancer patients to prevent muscle atrophy[4][5]. Several randomized trials aimed to increase muscle mass by administering androgen receptor agonists, anabolic nutrition/supplementation, or combined pharmacological treatments involving nutrition and anti-inflammatories with or without exercise failed to reduce sarcopenia significantly[6][7]. This is unsurprising as sarcopenia is a complex and separate physiopathological condition that involves the loss of skeletal muscle form and function[8].

An additional issue with the trial results is that at 8 weeks, the authors evaluated 29 patients from the placebo arm and 35 patients from the mirtazapine arm (Table 2). However, as the authors stated in Figure 1 (Consort flow diagram), there were only 27 (not 29) in the placebo arm and 31 (not 35) in the mirtazapine arm. Moreover, regarding the energy and carbohydrate intake at 4 weeks, the authors state in the text that 33 and 38 patients were evaluated at this point in time; however, in Table 3, the numbers were 31 and 34. Among the fat intake at 8 weeks, the numbers in Figure 1 are 31 and 37, while Table 3 shows 26 and 27. In both the 4- and 8-week evaluations, these numbers suggest selective reporting, which raises doubts about the validity of the data and impacts the conclusions drawn from the study.

More worrisome, almost no side effects were reported in this study. Accordingly, there were no cases in either group of somnolence or the perception of drowsiness, dizziness, anxiety, tremors, or insomnia, which sharply contrasts with Hunter's study[9]. Hunter et al., using 15 mg daily of mirtazapine, reported that less than half (29/60, 48%) of patients allocated to the mirtazapine arm completed eight weeks of treatment and that nine (15%) of the arm discontinued mirtazapine because of grade 3-4 sleepiness in 6 (10%) and visual hallucinations in 3 (5%).

Conclusions

The conclusions of this study, stating that mirtazapine may represent an accessible and well-tolerated option to treat NSCLC with sarcopenia, need to be reconsidered. This is also a reminder to the editor of JAMA Oncol of the need for very stringent peer review to ensure that publications meet the highest standards. This is not only an imperative for science but also for patients to avoid exposing them to drugs with unclear benefits but with potential side effects. It also highlights the urgency of more comprehensive studies in this area.

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