



Should Loss of Appetite Be Palliated in Patients with Advanced Cancer?

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This article is part of the Topical Collection on *Palliative and Supportive Care*

Keywords Loss of appetite · Cancer · Anorexia · Palliation

Opinion statement

Loss of appetite is common among patients with advanced cancer. However, it remains controversial how, when, and if to palliate this symptom. Here, we provide an update on recent as well as past literature to address the question of whether loss of appetite should be palliated in patients with advanced cancer. In our opinion—and as discussed here—we believe that this symptom should be palliated, although perhaps not always with pharmacologic interventions.

Introduction

The question posed in the title of this article reflects the question that arose upon reading two recent publications. This first publication is the American Society of Clinical Oncology guideline entitled, “Management of Cancer Cachexia” [1••]. Acknowledging the limitations of current palliative interventions for this syndrome of “cancer cachexia,” the authors conclude with the following recommendations: “Dietary counseling may be offered.... [but] no specific pharmacological interventions can be recommended.” The second publication focuses on palliative care. Previous studies suggest that palliative

care—in effect, attempting to palliate any and all symptoms in patients with advanced cancer—results in favorable outcomes, including an improvement in survival. However, in this second publication, Temel and others reported on a multi-site trial from the Alliance for Clinical Trials in Oncology [2••]. This 391-patient trial tested early integrated palliative care plus oncology care versus usual oncology care. The trial focused on quality of life as the primary endpoint, sought an improvement from baseline to week 12, but did not achieve its intended goal. Specifically, Temel and others reported

on a 3.35 mean increase (standard deviation: 14.7) in FACT-G scores from baseline in the intervention group and a 0.12 mean increase (standard deviation: 12.7) in the standard care group, resulting in no statistical significance difference between these two arms ($p=0.10$). Of note, this trial did not specifically focus on palliating

loss of appetite, but, in keeping with prior such research, appeared assessed a multitude of symptoms—under the auspices of “palliative care”—with a focus on palliating all symptoms. Thus, in this context of these two recent publications, the question of whether or not to palliate loss of appetite remains open for further discussion.

Loss of appetite, its prevalence, and its ramifications

Loss of appetite is a prevalent symptom in patients with advanced cancer. Previous studies suggest that the majority of patients with advanced cancer suffer from loss of appetite. For example, Mavros and others studied 10,753 patients with pancreas cancer and reported that 54% suffered from loss of appetite [4]. Enhancing our understanding of the prevalence of this symptom, Rha and others recently examined loss of appetite as a symptom cluster from a time standpoint and with respect to chemotherapy administration [5]. Analyzing 249 cancer patients who had participated in a previously reported clinical trial, these investigators identified loss of appetite as one of the three most predominant set of symptom clusters alongside anxiety/depression and fatigue. Interestingly, although loss of appetite was sometimes present at baseline, it appeared to peak in a cyclical manner that coincided with the administration of chemotherapy. This study included patients with a wide range of cancer types as well as patients with both potentially curable and incurable cancer. However, despite the heterogeneity of this patient sample, a clear signal pointed to loss of appetite as one of the most common symptoms among cancer patients. Of timely note, a relatively small study from Grover and others examined hospitalized patients with gastrointestinal malignancies and with a concurrent diagnosis of COVID-19 [6]. These investigators noted that the majority of these patients were also suffering from loss of appetite. Taken together, these studies clearly show that loss of appetite continues to be prevalent among cancer patients, thus emphasizing the need to continue to focus on this symptom from both a clinical and research perspective.

More recent research has focused on symptom complexes, describing a series of related symptoms such as early satiety, changes in taste and smell, and diurnal changes in food intake [7]. Although some clinicians view all these symptoms as distinct, patients might well be blending these together in their minds. Thus, it appears prudent for clinicians to tease out certain interrelated symptoms that might be amenable to other specific palliative treatments.

Importantly, loss of appetite has serious ramifications; for one, it predicts poor survival in patients with cancer. For example, Shimose and others examined the use of the agent lenvatinib in patients with hepatocellular carcinoma [8]. The median survival of patients who developed loss of appetite compared with those who did not was 15.1 months versus not reached ($p=0.01$). Although these investigators were reporting on only associations, they did go on to point out that loss of appetite appeared to have driven lenvatinib discontinuation. This limited exposure to this antineoplastic agent appears, in turn, to have resulted in limited benefit to patients who were forced to discontinue this

agent. These investigators also described how baseline loss of appetite predicts poor survival, underscoring the well-accepted concept that the underlying cancer can in fact be a major driving force behind this previously described symptom-driven prognostic effect [9].

In addition to its negative impact on survival, loss of appetite has other negative ramifications [10]. Importantly, patients are distressed by their loss of appetite and weight. Hopkinson illustrates this point well by means of qualitative research or patient interviews that seek to understand the patient experience [11]. One such patient commented with the following:

This bony thing shows up in the mirror every morning, and my eyes fall on this creature on the other side of the mirror. I was five feet from him before he could figure out who it was. I cried, because he was a very, very good friend of mine. It seemed to confirm that fact that I was so skinny.

Moreover, failed attempts on the part of family members to entice patients to eat can be painful for all involved. For example, in another study, Hopkinson again used qualitative methods to interview family members of cancer patients; direct quotations from these family members illustrate the challenges that family members face [12]:

You've been trying to look after him, to then have someone coming in with 'well do you do this and do you give him that?' and in a lot of instances some of the things they (dietician) suggested I know he wouldn't eat anyway.... A child yes you can try and encourage them and push it down can't you. But I don't think you can somebody his age.... There was a lack of credit to the fact that I actually know him an awful lot better than they did!

Clearly, the prognostic ramifications—coupled with the significant psychological distress patients and family members experience—underscore the conclusion that loss of appetite carries markedly negative implications for patients with advanced cancer.

Can loss of appetite be palliated?

Yes, this symptom can be palliated. The first and largest randomized, placebo-controlled trial to test a commonly used agent, megestrol acetate, demonstrated favorable improvements in appetite. This trial recruited 133 cancer patients, prescribed megestrol acetate at a dose of 800 mg/day to approximately half of them, and assessed palliative outcomes by means of patient-reported questionnaires and other indicators [13]. This study concluded that appetite improved in those patients who were prescribed megestrol acetate: 63% versus 39% ($p=0.003$). Placebo-controlled trials have also demonstrated that corticosteroids at doses of 1–2 mg twice per day are also efficacious for the palliation of loss of appetite [14]. Interestingly, the first placebo-controlled trial for loss of appetite in cancer patients tested corticosteroids. In this trial entitled "Corticosteroid therapy for preterminal gastrointestinal cancer," Moertel and others administered two doses of dexamethasone—0.75 mg and 1.5 mg—four times per day to 116 cancer patients. These investigators observed an improvement in appetite and sense of well-being among dexamethasone-palliated patients, but

survival and related endpoints were not favorably impacted [14]. Building on these landmark studies, multiple other studies have confirmed that both progestational agents and corticosteroids can serve a palliative role with respect to improvement in appetite, although improvements in survival and quality of life have not been demonstrated [15–17].

Which of these two classes of agents is the preferred palliative agent for appetite loss in patients with advanced cancer? A randomized trial studied this question, comparing dexamethasone ($n=158$) and megestrol acetate ($n=158$) for cancer-associated loss of appetite (another arm included fluoxymesterone, which was ineffective and therefore will not be discussed here). Both these agents improved appetite, but dexamethasone yielded worse short-term adverse events (36% versus 25%; $p=0.03$), such as Cushingoid changes, insomnia, peptic ulcer disease, and myopathy [17]. Thus, for long-term use, megestrol acetate, which admittedly does have a notable adverse event profile that includes blood clots, adrenal insufficiency with abrupt discontinuation, menstrual bleeding with abrupt discontinuation, and male impotence (among others), is the preferred pharmacologic intervention.

Both megestrol acetate and corticosteroids are older agents, and recent data suggest that other agents may be considered in the future for appetite stimulation. Another robustly studied pharmacologic agent is anamorelin hydrochloride, an oral ghrelin receptor agonist. In a 900+ patient study, anamorelin hydrochloride showed improvement in appetite as a non-primary endpoint [18]. However, this agent is not included in the current discussion as a viable palliative option because FDA-approval has not yet been granted. Alternatively, Navari and others recently reported on a small, double-blinded, placebo-controlled trial that studied olanzapine for chronic nausea [19••]. As a secondary endpoint, anorexia was evaluated. Interestingly, not only did olanzapine palliate nausea, but it also helped with loss of appetite. This trial included a small sample size and, as noted, improvement in appetite was detected as only a secondary endpoint. In yet another study, Navari and others reported on how olanzapine improves anorexia more effectively than megestrol acetate. However, in this second study, megestrol acetate performed less effectively than it typically does, an observation which appeared to lessen enthusiasm for olanzapine as an appetite stimulant in cancer patients [20]. Therefore, although further study of olanzapine is necessary to define it as an additional pharmacological intervention, these preliminary findings appear promising. Although we continue to think that further study is necessary, some clinicians might consider olanzapine as an appetite stimulant in select patients with cancer.

Of interest, omega-3-fatty acids are another group of agents that have received intermittent interest as an appetite stimulant [21–25]. Although some would argue that, in view of the limited side effect profile of omega-3-fatty acids, these agents should be prescribed for poor appetite; in our opinion, larger studies have pointed to less favorable orexigenic effects compared with the agents above [15]. Furthermore, these agents can cause belching and flatulence, suggesting that other approaches might be preferable.

But should loss of appetite be palliated?

Despite observations that loss of appetite is associated with compromised quality of life and survival, to date, no pharmacological intervention has

demonstrated a clearly favorable impact on global quality of life or on survival. In fact, an earlier meta-analysis questions whether megestrol acetate is associated with early death [26]. This 2013 Cochrane review from Ruiz-Garcia and others showed a risk ratio of 1.42 ($p < 0.05$) for death among patients who received megestrol acetate for appetite stimulation [26]. Trends suggested a higher risk of death with higher doses of this hormonal agent. However, this observation of early death remains controversial. Indeed, Ruiz-Garcia and others described their unexpected observation with the appropriate degree of prudence: "This conclusion should be taken with caution, however, because the severity of illness in these patients is high and they have a high risk of death... none of these trials included in the review were designed to investigate mortality as primary endpoint and duration of follow up was very short in most, so this unexpected result requires serious additional research..." Furthermore, observations from others—albeit in the context of cancer treatment with megestrol acetate—only further underscore the controversial nature of this risk of early death. For example, Muss and others observed a survival advantage with higher doses of megestrol acetate in patients with advanced breast cancer and concluded that "High-dose megestrol acetate resulted in a superior... survival (median, 22.4 months versus 16.5 months)..." [27]. Although it might be possible that an agent can reduce survival when used for one clinical indication, such as symptom palliation, and improve survival when used for another clinical indication, such as cancer treatment, these contradictory scenarios seem somewhat unlikely. Nonetheless and in essence, we believe that the real issue as to whether to treat or palliate cancer-associated anorexia does not center on harm from these pharmacological agents, but rather on whether pharmacological interventions are truly the best modality for attempting to palliate loss of appetite in patients with advanced cancer.

Interestingly, along these lines, Ukovic and Porter recently provide a systematic review that showed dietary counseling comprised another intervention that appears to help cancer patients with loss of appetite [28]. Similar to palliative care, a short-coming in such studies is a lack of granularity in methodology that provides healthcare providers sufficient detail on how best to implement this intervention—in this case, dietary counseling—to yield a favorable outcome. Nonetheless, dietary counseling has been suggested as a beneficial intervention by these investigators and others [29].

Another important point revolves around family members. Previous studies have shown that loss of appetite and the fact that patients are unable to participate in meals bothers family members. Sarhill and others have pointed out that sometimes, the patient's family—as opposed to the patient himself/herself—is suffering. Under these circumstances, extra time with and attention to family members is necessary to help all involved understand loss of appetite, its implications, and the fact that family members should not be blaming themselves for the patient's poor food intake [30].

In summary, we believe that the decision on whether to palliate loss of appetite should focus on thoughtful discussions between healthcare providers, patients, and their families. If an improvement in appetite—even transient of only a few weeks—is meaningful to a patient and his/her/their family, then the use of one of the pharmacologic agents above is indicated. If, in contrast, a modest, short-lived improvement in appetite does not seem meaningful to the patient, then other interventions—such as in-depth discussions and dietary counseling with a focus on small meals, supporting the patient to do his/her/their best, diverting focus away from quantity of food consumed and weight loss, and directing focus towards

patient comfort and meaningful time spent with family members—should be pursued. In essence, we believe that loss of appetite should always be palliated, although not necessarily with pharmacological interventions.

Acknowledgements

Dr. Jatoi is the Betty J. Foust, M.D. and Parents' Professor of Oncology

Code availability

Software code is not applicable.

Author contribution

The authors contributed equally to this work.

Data availability All data generated or analyzed during this study are available from the corresponding author on reasonable request.

Compliance with Ethical Standards

Ethics Approval and Consent to Participate

Not applicable. Consent to participate is not applicable.

Consent for Publication

Not applicable

Conflict of Interest

Christopher Ehret declares that he has no conflict of interest. Aminah Jatoi declares that he has no conflict of interest.

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