Lung Cancer 112 (2017) 25–34

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Research paper

Anamorelin for advanced non-small-cell lung cancer with cachexia: Systematic review and meta-analysis

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ARTICLE INFO

Keywords:
Non-small-cell lung cancer
Anamorelin
Cachexia
Weight loss

ABSTRACT

Introduction: Cancer anorexia-cachexia syndrome (CACS) is characterized by involuntary weight loss. CACS is commonly observed in advanced non-small-cell lung cancer (NSCLC), and it leads to a poor quality of life (QOL). No effective standard treatment exists for this condition. However, anamorelin has reportedly caused improvement in patients with several cancers.

Materials and methods: We conducted a quantitative meta-analysis to explore the efficacy of anamorelin for treating CACS in patients with NSCLC. We systematically searched CENTRAL, MEDLINE, EMBASE, CINAHL, and OvidSP. We pooled the data and calculated and compared total body weight (TBW), lean body mass (LBM), overall survival (OS), hand grip strength (HGS), QOL, and adverse events (AEs) between patients treated with anamorelin (anamorelin group) and those not (placebo group).

Result: Six randomized controlled trials included 1641 patients with NSCLC. Both TBW and LBM were significantly increased in the anamorelin group compared to the placebo group (mean differences [MD] 1.78, 95%CI: 1.28–2.28, $p < 0.00001$; MD 1.10, 95%CI: 0.35–1.85, $p = 0.004$, respectively). The groups showed no difference in OS or HGS (hazard ratio 0.99, 95%CI: 0.85–1.14, $p = 0.84$; MD 0.52, 95% CI: −0.09–1.13, $p = 0.09$, respectively). Anamorelin significantly improved the QOL (standardized MD 0.19, 95%CI: 0.08–0.30, $p = 0.0006$). The frequency of any AEs and grade 3 or 4 AEs were not significantly different between groups (risk ratio[RR] 1.03, 95%CI: 0.95–1.10, $p = 0.49$; RR 0.86, 95%CI: 0.48–1.54, $p = 0.62$).

Conclusion: This analysis demonstrated that anamorelin represents a promising treatment option for CACS in patients with advanced NSCLC.

1. Introduction

Cancer anorexia-cachexia syndrome (CACS) is a multifocal disease associated with increased morbidity and mortality, poor quality of life (QOL), and poor treatment outcomes [1,2]. CACS was estimated to occur in 50–80% of patients with cancer, and it is more commonly observed in lung and gastrointestinal cancers [1,3]. CACS is characterized by involuntary weight loss, defined as more than 5% loss within 6 months or more than 2% loss in patients with a low body-mass index (BMI, < 20 kg/m^2) [4]. Weight loss is observed in about 60% of patients with lung cancer at the time of diagnosis, [5] and it indicates a poor prognosis [6,7]. Thus, non-small-cell lung cancer (NSCLC) is a debilitating disease, and QOL is an important factor in the treatment [8,9]. Treatment goals in CACS include improvements in appetite, lean body mass (LBM), resting energy expenditure, QOL, performance status (PS), and inflammatory status [10]. Many therapies have been tested for overcoming CACS, but currently, there is no standard of care or effective treatment [4,11].

Ghrelin is a neuropeptide produced by ghrelinergic cells in the gastrointestinal tract. Ghrelin agonist also induce growth hormone (GH) secretion and insulin-like growth factor-1 (IGF-1) [12]. The GH and IGF-1 increase LBM and fat mass not only by stimulating appetite but also by preventing energy consumption. [13–15] It was contrary with corticosteroids and progestational drugs, which only stimulate appetite and total body weight (TBW). [16] Plasma ghrelin concentration reported in cancer patients was various. In patients with lung cancer, some reports indicated that the ghrelin concentration was increasing in comparison with that in controls [17]. Ghrelin also showed

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http://dx.doi.org/10.1016/j.lungcan.2017.07.023
Received 20 April 2017; Received in revised form 14 July 2017; Accepted 18 July 2017

anti-inflammatory effects in a murine model of cancer cachexia [18]. Therefore, ghrelin mimetics have been regarded a promising approach, and they are currently under study for their potential impact on CACS.

Anamorelin (ONO-7643) is an orally administered low molecular-weight ghrelin agonist. [19] Randomized controlled trials (RCTs) of anamorelin showed that a 12-week treatment was well tolerated and significantly improved LBM, TBW, QOL, and appetite, compared to placebo in patients with NSCLC. [12,20,21] In trials of anamorelin in patients with advanced NSCLC, patient backgrounds were well balanced between randomized groups, but the groups showed differences in the prevalence of chemotherapy treatment, emetic risk with chemotherapy, the line of therapy, and mortality within 12 weeks. Thus, the efficacy of anamorelin in patients with NSCLC remains unclear in clinical settings. Evidence that supports the efficacy of anamorelin against CACS may provide a basis for developing a new management strategy for cachexia. In the present study, we conducted a systematic review and meta-analysis to assess the efficacy of anamorelin for treating cachexia due to NSCLC. The endpoints of this study were the effects of anamorelin on TBW, LBM, QOL, and adverse events (AEs) in patients with NSCLC and CACS.

2. Materials and methods

2.1. Search methods for identification of studies

This meta-analysis was carried out according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) Statement [22]. We conducted searches for studies with inceptions up to December 2016, in the following electronic databases: Cochrane Central Register of Controlled Trials (CEN-TRAL), MEDLINE, EMBASE, CINAHL, and OvidSP. We also searched the abstracts and meeting presentations in the American society of clinical oncology (ASCO) and European Society for Medical Oncology (ESMO) references through December 2016 by utilizing the same search terms. The search strategy was based on discussions with an information specialist, and it was appropriately modified for each database. The search strategy included a combination of free text words, words in titles/abstracts, and medical subject headings, including “Anamorelin”, “ONO-7643”, “cachexia”, “cancer” (Appendix A). Searches were limited to peer-reviewed research involving human participants. Different terms and spelling variations used in other countries were included in the search strategy to ensure that the search captured all potentially relevant studies on the topic. No language restrictions were applied.

2.2. Inclusion and exclusion criteria

We included all published and unpublished randomized controlled trials that evaluated the efficacy of anamorelin for CACS in patients with advanced NSCLC. Studies that only published an abstract were included when sufficient information was available for both the risk of bias assessment and the meta-analysis. In this review, we targeted patients with pathologically-confirmed NSCLC at an advanced stage (i.e., stage IV) that exhibited CACS. The primary outcome was TBW. Secondary outcomes included LBM, OS, HGS, QOL, and AEs.

Eligible studies were required to meet all the following criteria: (1) study design was an RCT; (2) study involved patients with confirmed advanced NSCLC and CACS; (3) study compared anamorelin and placebo; (4) study reported on at least one of the above outcome measures; (5) clinical data were available at 12 weeks after treatment initiation. We excluded animal studies and in vitro studies.

2.3. Data extraction

Two investigators (KN and SY) independently screened the titles and abstracts that included the key terms to determine relevance. Then, full texts of relevant articles were retrieved to assess eligibility. Any disagreements were resolved through consultation with the third author (MH) and discussion. The following information was recorded for each study: details of the intervention and the comparison method; number of patients randomly assigned to each group and attrition; outcome data; first author’s name; year of publication; trial phase; masking; underlying malignancy; patient age; and the follow-up duration. When insufficient data were available, we contacted the authors and requested unpublished data, or we estimated data, based on other available summary statistics or from data in published figures. All data were collected on an intention-to-treat basis, where possible.

2.4. Assessment of risk of bias in included studies

KN and SY independently assessed the quality of each study with the risk of bias tool in the Cochrane Handbook for Systematic Reviews of Interventions [23]. The risk of bias was assessed based on the following criteria; Random sequence generatio, Allocation concealment, Blinding of participants and personnel, Blinding of outcome assessment, Incomplete outcome data, Other bias.Conflicts were resolved by deiscussion with the third author (MH)

2.5. Meta-analysis and subgroup analysis

Participants were divided into two groups; the anamorelin group and the placebo group. The anamorelin group was further subdivided into two subgroups, according to the doses of anamorelin they received (100 mg and 50 mg) for subgroup analyses. Data synthesis and analyses were performed with Review Manager (RevMan) version 5.3. Continuous outcome measures were expressed as the mean differences (MD), when the results were measured in the same way in differenet studies. The mean and median are different concepts and often represent different values. Therefore, we considered that analysing by mixing the mean and the median value leads to erroneous results. The standardized mean difference (SMD) was used when the results obtained were conceptually the same, but used different measurement scales. When the change in SD for each group was not available, it was reconstructed from the standard error (SE) with the RevMan calculator. OS was calculated as the hazard ratio (HR) based on data from published studies. We calculated the pooled HRs for outcomes with an inverse variance method. The risk ratio (RR) was used to assess AEs.

We assessed statistical heterogeneity in each meta-analysis with Tau^2, I^2, and Chi^2 statistics following the Cochrane Handbook for Systematic Reviews of Interventions [24]. We regarded heterogeneity as substantial when I^2 was greater than 30% and either the Tau^2 was greater than zero, or the p-value was less than 0.10 in the Chi^2 test for heterogeneity. Data from each study were pooled with fixed-effects modeling, when no heterogeneity existed ($p > 0.1$, $I^2 \leq 40\%$). We performed meta-analyses with random-effects models when heterogeneity existed ($p < 0.1$, $I^2 > 40\%$).

To increase the validity of the results of the test, we performed a sensitivity analysis. All confidence intervals (CIs) had two-sided probability coverage of 95%. A p-value less than 0.05 was considered significant. When 10 or more studies were included in a meta-analysis, we created a funnel plot and examined its asymmetry visually to explore any publication bias. When there was a high risk of bias that could affect the results, we carried out a sensitivity analysis. A high risk of bias was defined as: (1) inadequate random sequence generation, (2) inadequate allocation concealment, or (3) more than 20% of data missing [25].

3. Results

A total of 120 records were identified in the initial search, according to the search strategy [26]. In addition, we found two other studies through annual meetings of the ESMO and ASCO. [27,28] Forty-two studies were excluded because they were duplicates. Fifty-two studies