Review Article

Pharmacological Management of Bronchorrhea in Malignant Disease: A Systematic Literature Review

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Abstract

Context. Malignant respiratory tract tumors can lead to massive fluid production, known as bronchorrhea. This symptom can be very distressing itself, and it can lead to or aggravate other symptoms such as dyspnea and cough. Pharmacological treatment options have been reported in the literature. However, no systematic evaluation of their effectiveness has been conducted so far.

Objectives. To systematically identify, appraise, and evaluate the effectiveness of symptomatic pharmacological treatment of bronchorrhea in malignant disease in palliative care.

Methods. A systematic literature review in Medline, Embase, and the Cochrane Database, as well as citation tracking, hand searches of selected journals, and reference lists of retrieved articles, was performed. For the purpose of this review, only symptomatic treatments were considered.

Results. No controlled clinical studies could be identified. Twenty of 48 retrieved references were analyzed in detail. These 20 case reports and case series dealt with the symptomatic pharmacological management of bronchorrhea in malignant disease; the other 28 had to be excluded for various reasons. The majority of patients suffered from bronchioloalveolar carcinoma. Reported treatments comprise corticosteroids, macrolide antibiotics, inhaled indomethacin, octreotide, and tyrosine-kinase inhibitors. For some drugs, significant clinical impact on distressing symptoms associated with bronchorrhea was reported.

Conclusion. There are only very limited data on the pharmacological management of bronchorrhea in malignant disease. Because of the distressing nature of the symptom, a pragmatic management strategy is essential. This can include promising treatment options reported in the literature but should also take into account availability, individual tolerability, and costs. Further research is needed. J Pain Symptom Manage 2016;51:916–925.

Key Words
Bronchorrhea, adenocarcinoma, sputum production, malignancy

Introduction

Respiratory mucus serves a variety of functions, primarily as medium for the transport and removal of particles, cells, and so forth, to the upper airways and mouth.[1] Expectorated sputum is usually a combination of upper and lower respiratory tract mucus and consists of proteins, glycoproteins, water, electrolytes, and lipids.[1,2] Bronchorrhea is defined as the excess production of watery sputum (≥100 mL/day).[3] It has been reported in association with lung diseases such as tuberculosis, chronic bronchitis, asthma, bronchiectasis, or malignant disease in the lung or metastatic to the lung.[2] In bronchioloalveolar carcinoma (BAC), the incidence of bronchorrhea is estimated to be 6%.[4] Although already very distressing by itself, bronchorrhea also may induce or worsen dyspnea,[5–7]

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hypoxemia,[8,9] salt and volume depletion,[5,7,10] and weakness.[6] Although single experiences with drug treatment have been reported in the literature, no systematic analysis of available data for the treatment of bronchorrhea is available. We, therefore, aim to identify, critically appraise, and assess the effectiveness of symptomatic pharmacological treatment options for bronchorrhea in malignant disease.

Methods

A systematic literature review was conducted according to the guidance of the Centre for Reviews and Dissemination.[11]

Search Strategy

An iterative approach was used starting with an electronic search of the databases Medline (via Ovid; 1946 to July Week 2, 2015), Embase (via Ovid, 1988 to 2015, Week 29), Biosis Previews (via Web of Knowledge, 1926–2009), and the Cochrane Central Register of Controlled Trials (Issue 6, 2015). The search terms "bronchorrhea (keyword)" AND "neoplasms (MeSH heading)" OR "malignant (keyword)" OR "tumour (keyword)" OR "cancer (keyword)" AND "management (keyword)" OR "treatment (keyword)" were used. The search was limited to "human," adolescent and adult patients (≥16 years). Furthermore, tables of content of highly ranked journals in palliative care and respiratory medicine were hand searched (Journal of Pain and Symptom Management, Palliative Medicine, Supportive Care in Cancer, Thorax, Chest, American Journal of Respiratory and Critical Care Medicine). The reference lists of pertinent publications retrieved from the database or hand search were screened for further relevant publications. Citation tracking and search for related articles in PubMed and Ovid was performed.

Study Inclusion and Exclusion Criteria

Inclusion criteria were as follows: patients aged older than 16 years, bronchorrhea as a result of malignant disease of the respiratory tract (primary tumor or metastases), all types of studies (randomized controlled trials, controlled trials, case reports, and case series).

We included case series and case reports in this review despite the risk of bias because an initial database search indicated a potential paucity of randomized controlled trials or other clinical trials.

Exclusion criteria were as follows: bronchorrhea in patients with coexisting malignant and nonmalignant disease that has already caused mucus hypersecretions in the past, and acute respiratory tract infection (e.g., pneumonia) that could potentially contribute to bronchorrhea. The focus of this review was symptomatic treatment and not treatment of the underlying disease. When retrieved literature addressed both, this was acceptable and the publications were taken into consideration. If possibly appropriate for the review, the full texts of the articles were obtained. The assessment of the literature was performed by two of the authors (C. R. and C. B.).

Data Extraction

As only case series and case reports could be identified, the use of the Centre for Reviews and Dissemination's template[12] for data extraction was not applicable. Instead, the following information was extracted in an Excel sheet by one author (C. R.) and checked by a second author (C. B.): patient characteristics, type of treatment, duration to treatment onset, duration of follow-up, and outcomes.

Results

The initial search yielded 48 articles. Sixteen publications did not address a specific pharmacologic treatment for bronchorrhea. The other publications were excluded for various reasons (Fig. 1). The remaining 20 publications were case reports ($n = 15$) and case series ($n = 5$) of 30 patients in total.

Details of the reported cases are summarized in Table 1. The majority of published cases were on patients with bronchorrhea as a complicating symptom of BAC. Only two of the 30 patients had malignancies of the pancreas and the cervix, respectively, but with metastasis of the primary adenocarcinoma to the lung in both cases.[7,19]

The majority of the published cases described the use of inhaled indomethacin ($n = 10$)[14–16] followed by cases on the use of gefitinib ($n = 9$),[26–31] a tyrosine-kinase inhibitor (TKI). Other reported treatments include octreotide ($n = 3$),[7,21,22] erlotinib ($n = 4$),[9,23–25] erythromycin ($n = 2$),[19,20] steroids ($n = 1$),[17] and a combination of clarithromycin and beclomethasone ($n = 1$).[18] The reported onset of action was within hours to about three days in all treatments. However, the effects were sometimes small and not sustained.

Inhaled Indomethacin

Although most cases ($n = 10$) were reported for the use of inhaled indomethacin, few details about the treatment were provided for seven of these cases.[16] Compared with other treatments, indomethacin had a relatively slow onset of action over a period of five days, and taking about a month until reaching its maximum effect.[15] The duration could potentially be lasting, as in the two cases described by Homma et al.,[15] where it controlled sputum production over months.