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Putting into Evidence: The Effect of Oral Glutamine on Radiation-induced Esophagitis among Patients with Lung Cancer

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Abstract

Oral glutamine supplementation is highly effective in preventing and delaying radiation-induced esophagitis, one of the most common discomforting side effects of radiation to the thoracic area among lung cancer patients. According to the literature, lung cancer is the leading cause of death among all cancers with the highest incidence worldwide. This paper aims to emphasize the importance of oral glutamine supplementation in preventing radiation-induced esophagitis among lung cancer patients. Several databases have been searched and seven studies included in this review (five randomized control studies, one quasi-experimental study and one systematic review) with a total of 453 patients. The patients in these studies were diagnosed with lung cancer regardless of type or stage. The patients were either assigned to an intervention group (glutamine supplementation) or a control group. These studies were conducted in the US, Turkey, Spain, and Greece from 2003 until 2012.

The results showed that 10 mg of oral glutamine three times per day on a daily basis (from one month before starting radiation until one month after completion of radiation)was effective in preventing and delaying radiation-induced esophagitis.

Keywords: Radiation-induced esophagitis, Lung cancer, Glutamine, Radiation toxicity, Thoracic radiation

Introduction

Glutamine is the most abundant free amino acid in the human body. The skeletal muscles considered to be the primary source of glutamine from where it is released into the bloodstream and transported to a variety of tissues. Glutamine plays an essential role in the promotion and maintenance of the function of various organs and cells. Moreover, it is an important precursor of peptides, proteins, amino sugars, purines, and pyrimidines because it is used in the synthesis of nucleotides and nucleic acids.[1] Glutamine constitutes 60% of the total free amino acid pool in the skeletal

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muscle. This amino acid has a direct relationship with symptoms associated with chemo/radiotherapy administration. Patients with different types of cancers have marked glutamine depletion that develops over time. Cancer cachexia is marked by massive depletion of skeletal muscle glutamine.

One of the considerations related to administration of oral supplementation is the toxicity level. The safety of glutamine supplementation at these levels has been shown in a one dose–response study which has reported no evidence of any clinical toxicity or generation of toxic metabolites at doses up to 0.3 g/kg. Moreover, nitrogen retention was optimally enhanced at a glutamine dose of 0.57 g/kg per day.[2]

Because of the significance of glutamine in maintaining homeostasis of the body and prevention of the epithelial cell toxicity due to chemotherapy or radiotherapy, many studies have been conducted on the importance of glutamine among cancer patients. A study on protecting healthy body tissues from the adverse effects of radiotherapy among patients with bladder cancer has shown that glutamine played a key role in prevention of bladder wall damage in relation to extracellular matrix volumetric density and collagen expression.[1] Another beneficial use of oral glutamine supplementation concerned prevention of acute radiotherapy-induced esophagitis (ARIE) and weight loss among lung cancer patients undergoing thoracic irradiation.[3] This paper highlighted the importance of oral glutamine supplementation in preventing radiation-induced esophagitis among lung cancer patients.

Theoretically, supplemental glutamine can promote tumor cell growth because human tumors exhibit a 5- to 10-fold faster rate of glutamine consumption than normal healthy tissues. However glutamine does not stimulate tumor growth, nor does it negatively affect the outcome of any type of anti-tumor treatment. Both Topkan et al.[4] and previously published reports have assured the safety of this type of supplementation.

Lung cancer is the leading cause of cancer death in the United States with a cure rate of less than 15%. One of the main side effects of lung cancer radiotherapy treatment is radiation-induced esophagitis.[5] Other studies have also shown variations in radiation-induced esophagitis. Severe acute esophagitis (grade 3 or higher) is encountered in 1.3% of patients treated with standard thoracic radiation therapy, in 6% of patients who receive induction chemotherapy followed by standard radiation therapy, and in 34% of those treated with concurrent hyperfractionated radiation therapy and chemotherapy.[6]

Furthermore Jazieh et al.[5] and Werner-Wasik et al.[6] agree that radiation-induced esophagitis may cause significant morbidity and unplanned treatment delays in patients with lung cancer. Such complications not only impact patient quality of life but also reduce the ability to escalate the radiation therapy dose to more effective levels. This results in potential reductions to tumor control and survival rates. Consequently, radiation-induced esophagitis may deteriorate the patient's quality of life, something which must be monitored and is of more concern among lung cancer patients. Monitoring of radiation-induced esophagitis is intended to decrease mortality and morbidity among those patients.

Unfortunately, despite the beneficial, safe use of oral glutamine to protect against radiation-induced esophagitis among patients undergoing thoracic radiation, there are only a limited number of clinical trials that have considered this supplementation as a preventive procedure before thoracic radiation. According to Riaz et al.,[7] lung cancer is the second most common cancer among males and females in the UK. However it has a cumulative lifetime risk of 5% for males and 3% for females. Lung cancer is divided into two groups, small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). SCLC comprises approximately 20% of all recorded lung cancer cases.[7]

More than one-third of patients with NSCLC present with locally advanced, unresectable tumors. Concurrent radiation and chemotherapy

is the treatment of choice in these patients. However, this treatment is associated with a high risk of toxicity which can not only negatively impact quality of life, but also can affect treatment efficacy through the recurrent necessity for hospitalizations and treatment breaks. Prior published studies have shown that this treatment is associated with a high risk of toxicity from high-grade radiation-induced esophagitis during radiation.[8] Radiation administered to the chest area can lead to significant, dangerous side effects such as radiation esophagitis, which may prevent continuation of radiotherapy and limit food intake which results in severe nutritional deficiencies.

Prevention of radiation-induced esophagitis is the best way to avoid this problem. We searched numerous databases for related literature. Oral glutamine supplementation on a daily basis has been shown to be effective in the prevention or delay of the occurrence of radiation-induced esophagitis among cancer patients treated by radiotherapy to the thoracic area, with or without chemotherapy. Furthermore it can prevent any extra cost related to radiation toxicity. Unfortunately, few randomized clinical trials have considered this problem despite the fact that glutamine is an inexpensive, safe supplement that may be useful in preventing radiation-induced esophagitis.

This study evaluated evidence from the literature in order to illustrate the effectiveness of oral glutamine supplementation in preventing radiation-induced esophagitis among lung cancer patients.

Materials and Methods

Literature search

We conducted an extensive search of different databases such as CINAHL, ScienceDirect, EBSCO, and PubMed in order to extract the most updated randomized control study (RCT), quasi-experimental trials, and systematic reviews that discussed the effectiveness of glutamine in preventing radiation-induced esophagitis.

The inclusion criteria included: patient populations diagnosed with lung cancer regardless of the type or stage; the population group should have undergone either thoracic radiotherapy or chemo-radiotherapy; and a sub group of these populations should have received glutamine supplementation as a preventative treatment.

According to the inclusion criteria only seven studies were selected for this paper. Unfortunately, this limited number might have impacted the generality of the findings. These seven studies (five randomized control studies, one quasi-experimental study, and one systematic review) comprised a total number of 453 patients divided into intervention (glutamine supplementation) or control groups. These seven studies were conducted in the US, Turkey, Spain, and Greece during 2003 to 2012. Among these studies, the radiotherapy doses ranged from 44 to 60 Gy administered to patients with varying types and stages of lung cancer.

Results

A systematic review of a randomized control study has shown that the role of glutamine in the prevention of chemotherapy and radiation-induced toxicity is evolving. Glutamine supplementation is inexpensive and may reduce the incidence of gastrointestinal, neurologic, and possibly cardiac complications of cancer therapy.[2] This emphasizes the importance and significance of this issue. In support, a study of 41 lung cancer patients has shown that glutamine supplementation appeared to significantly delay ARIE onset for six days. Hence, glutamine might be of benefit in the prevention of ARIE and weight loss in lung cancer patients undergoing thoracic irradiation.[3]

Numerous studies have demonstrated the protective effect of glutamine on mucosa treatment by chemotherapy and radiation by three distinct mechanisms. Glutamine serves as a primary cellular fuel for enterocytes, it is a precursor for nucleotides necessary for cell regeneration, and a source of glutathione as a potent antioxidant.[1,3,5] The addition of glutamine did not protect fully against esophagitis.[5] In contrast to this finding it has been shown that glutamine appeared to have a beneficial effect with respect to prevention of

weight loss, unplanned treatment delays, and reduction in the severity and incidence of acute- and late esophagitis.[6]

According to Topkan et al.,[4] "There was no concurrent chemo-radiotherapy related the acute or late grades 3-5 toxicity level". Therefore, the administration of glutamine was associated with a decrease in the incidence of grade 3 acute radiation-induced esophagitis to 7.2% in the glutamine group versus 16.7% in the control group ($P<0.02$) and late radiation-induced esophagitis to 0% in the glutamine group versus 6.3% in the control group ($P<0.06$). They also reported a reduced need for unplanned treatment breaks [7.1% (glutamine) vs. 20.8% (control); $P<0.04$] and reduced incidence of weight loss [44.6% (glutamine) vs. 72.9% (control); $P<0.002$], which again illustrated the tremendous benefit of oral glutamine when administered to lung cancer patients prior to radio-chemotherapy.

Algara et al.[9] reported that no patient experienced glutamine intolerance or glutamine-related toxicity in their study. A total of 73% of patients who received sequential chemotherapy and 49% of those who received concomitant chemotherapy had no evidence of esophagitis.

The use of oral glutamine might have an important role in the prevention of esophageal complications of concomitant radio-chemotherapy in lung cancer patients. To emphasize, regarding the safety and lack of toxicity of glutamine, neither adverse effects nor toxicity have been registered as attributed to glutamine. In a study by Luna et al., there were 68 lung cancer patients (57 males and 11 females) enrolled of which 23 (34%) were diagnosed with limited small cell carcinoma and 45 (66%) with non-small cell carcinoma. In this study 53 (78%) received concomitant chemo radiation (group A) and 15 (22%) underwent sequential treatment (group B). The mean dose administered was 60 Gy, at a dose of 2 Gy per fraction, for five fractions per week. The results indicated a clear benefit for glutamine in the prevention of acute esophagitis in these patients who were treated with chemo/radiotherapy and were advised to take glutamine (10 g per dose every 8 hours) for at least five days before radiotherapy until fifteen days after completion of radiation therapy compared to those who did not use glutamine.[10]

Another study with 150 lung cancer patients showed that in the intervention group (glutamine) compared to the control group (no glutamine) , all the subjects which have taken glutamine, before, during and after the end of treatment (radio or chemotherapy) complained from esophagitis Grade I, mild pain, dysphagia Grade zero or one. But their symptoms relieved faster than the control group who did not take glutamine. While 25 subjects who have not take glutamine complained from esophagitis Grade II, also they need a longer time to recover from those symptoms. To sum up, there is a positive effect of glutamine when administered orally in prevention and the treatment of toxicity due to radio-chemotherapy in patients with lung cancer was shown. In addition, there is a clear benefit for using oral glutamine in reducing the occurrence of esophagitis after irradiation.[11]

Discussion

Oral glutamine doses of 10mg three times per day at a varying time periods from one month before thoracic radiotherapy to one month after completion of radiotherapy was efficacious in preventing and delaying radiation-induced esophagitis.

Glutamine is a safe, toxic-free drug. The results are important and significant for preventing and delaying radiation-induced esophagitis, which consequently improves quality of life and positively affects patient compliance to the treatment regimen. Unfortunately, only a few studies have been conducted that illustrate the effectiveness and importance of oral glutamine in preventing radiation-induced esophagitis after thoracic radiation. Therefore more studies are needed in this area.

Feasibility

Oral glutamine supplementation is recommended for daily use as a protector of radiation-induced esophagitis in order to enhance

quality of life, reduce the need for unplanned treatment breaks, and reduce the incidence of weight loss among cancer patients, as well as decrease possible associated costs associated with radiation-induced esophagitis. Finally, oral glutamine supplementations are available worldwide.

Limitations

Unfortunately the seven studies used in this analysis and critique were not specific in describing the location, population age (range: 18-68 years of age), and the small sample size in most studies which might have affected generalization of the results. Although one study included 150 patients, another study only included 15 patients. The treatment plans included in these studies combined chemotherapy in addition to the radiotherapy which might have limited the generalizations.

Conflict of Interest

No conflict of interest is declared.

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