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L-Glutamine and Oral Mucositis

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ABSTRACT

The term oral mucositis emerged in the late 1980s to describe the adverse effects of chemotherapy-induced and radiation therapy–induced inflammation of the oral mucosa. The ulcerative lesions produced by mucotoxic chemo radiotherapy are painful, restrict oral intake and, importantly, act as sites of secondary infection and portals of entry for the endogenous oral flora. Various approaches are available for the treatment of mucositis like antibacterial, antifungal, antiviral, cytoprotectants, immuno-modulatory, analgesic and some herbal extracts. It is very difficult for clinician to choose from this bewildering array of treatment options. Several studies have evaluated the benefit of oral or parenteral glutamine supplementation in cancer patients receiving chemotherapy and/or radiotherapy or after bone marrow transplant, with. L-glutamine is considerably reduce the duration and severity or oral mucosa during radiotherapy. L-glutamine is considerably reducing the duration and severity of oral mucosa during radiotherapy. L-glutamine decreases the side effects such as inflammation of mouth and throat caused by chemotherapy and radiotherapy

Keywords: Mucositis, L-Glutamine, chemotherapy, radiotherapy**.**

1. INTRODUCTION

Oral mucositis is a frequent and dose-limiting effect of chemotherapy. In patients receiving 5-FU, it has been estimated that as many as 40% may develop oral mucositis [1] High-risk protocols can produce severe mucositis rates in excess of 60% [2]. This condition is associated with discomfort symptoms, decreasing patients' quality of life, and increasing economic costs as well as risk of infection and sepsis [3] . Historically, mucositis was viewed solely as an epithelium-mediated event, which was the result of the nonspecific toxic effects of radiation or chemotherapy on dividing stem cells [4]. It was believed that direct damage by chemotherapy or radiation therapy to the basal epithelial cell layer led to loss of the renewal capacity of the epithelium, resulting in clonogenic cell death, atrophy, and consequent ulceration. New research, however, has suggested that mucositis is not just an epithelial process but involves all the tissues of the mucosa, as evidenced by recent data involving morphologic findings, proinflammatory cytokines, platelet aggregation, endothelial and connective tissue injury, and tissue apoptosis[3]. Approximately one-half of those individuals develop lesions of such severity as to require modification of their cancer treatment and/or parenteral analgesia. The conditions incidence is consistently higher among patients undergoing conditioning therapy for bone marrow/peripheral blood progenitor cell transplantation, continuous infusion therapy for breast and colon cancer, and therapy for tumors of the head and neck associating concomitant chemotherapy and radiotherapy. Among patients in the high-risk protocols, severe mucositis occurs with a frequency in excess of 60% [5] .

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Therapy for oral mucositis is limited to pain medications and treatment of secondary infection. In particular, recommendations have included treatment with topical anesthetics such as xylocaine, benzocaine and cocaine, treatment with solutions which coat the ulcerative lesions with a polysaccharide gel and use of antiseptic solutions such as Chlorhexadine. While all these treatments do provide some relief, none are directed to the actual healing of oral mucositis, which entails directly healing the mucosal epithelium cells.

Glutamine is the most abundant free amino acid in the human body and its flux between tissues is greater than that of any other amino acid [6.] It is essential for the growth of normal and neoplastic cells and for the culture of many cells types [7]. Several studies have evaluated the benefit of oral or parenteral glutamine supplementation in cancer patients receiving chemotherapy and/or radiotherapy or after bone marrow transplant, with conflicting results. Confirming a former non-randomized pilot study [8], the same research group published a randomized, double blind, crossover trial in cancer patients receiving chemotherapy which showed that oral glutamine appears to be useful to increase the comfort of patients at high risk of mouth sores as a consequence of chemotherapy [9]. Other studies also show that oral glutamine decreases the severity and duration of oropharyngeal mucositis in patients undergoing bone marrow transplantation [10]. However, there are also reports in which glutamine fails to alleviate oral mucositis in patients from bone marrow transplants and also in patients in use of 5-fluorouracil (5-FU) [11, 12, 13]. A recent double blind, placebo- controlled trial, in head and neck cancer patients treated with chemoradiotherapy, demonstrated that intravenous L-alanyl-L-glutamine reduced the number of patients with severe oral mucositis and that those in use of alanylglutamine experienced less pain compared to placebo treated group [14]. Glutamine was classified as a non-essential amino acid, but in more recent years it has been shown that despite a large repository of glutamine, stores may become depleted, particularly in the course of many catabolic assaults such as injury, infection, or chronic glucocorticoid treatment [15]. This appears especially important for susceptible individuals, such as postoperative patients, very low birth weight infants and individuals with cancer [16]. It has been demonstrated that tumor-growth depletes the host glutamine stores, resulting in cachexia [17]. Accordingly, patients with head-and-neck cancer are naturally depleted of glutamine [18], a condition that may be exacerbated by the effects of cancer treatment as suggested by data presented here. The demonstration that 5-FU induced glutamine depletion, prompts us to investigate the role of glutamine or alanyl-glutamine supplementation in the course of 5-FU induced oral Mucositis. In view of this, we would expect glutamine supplementation to have benefits in 5-Fluoro induced oral mucositis. Cysteine and other thiol compounds have been considered rate-limiting for glutathione biosynthesis, but it has been demonstrated that glutamine becomes essential during metabolic stress to restore tissue glutathione levels which have become depleted [19,20]. Different factors may be taken into account to explain the benefits of exogenous glutamine in hastening oral mucosa healing. First, it has been demonstrated that glutamine can activate ornithine descarboxylase, a first and rate-limiting enzyme in polyamine synthesis in a dose- and time dependent manner, thereby enhancing DNA synthesis. In addition, glutamine can activate mitotic signaling pathways, including mitogen-activated protein kinases and transcription factors, leading to proliferative responses [21, 22]. Second, previous studies have suggested that glutamine augments host defenses and may be important in glutathione synthesis thus decreasing the oxidative stress [23,24,25,26]. Glutamine is a neutral, non-essential amino acid. It is also the most abundant amino acid, comprising about 60% of the total free amino acid pool [27]. Glutamine contains two nitrogen moieties, and as such, it may also be one of the most versatile amino acid. Regular supplementation of glutamine (0.57 gm/kg body weight / day) not only heals the injuries but also strengthen the mucosa Thus it protects GI tract from devastating effects of chemotherapy and radiotherapy and patients don't experience mouth as well as abdominal pain [28]. Swish and swallow with glutamine drink will heal the injury and gives relief from the mouth pain. Oral glutamine might significantly reduce the duration and severity of oral mucositis during radiotherapy. It may shorten the duration of ≥ Grade 3 subjective mucositis. World Health Organization (WHO) step analgesic medication and body weight change were compared between the two arms. Mean maximum grade of objective oral mucositis was less severe in the glutamine arm (1.6 vs. 2.6) [29, 30]. In addition to this apparent mucosal protective effect, glutamine was also shown in an animal model to be a potential enhancer of chemotherapy [31]. However, despite these positive early findings, tests of glutamine in a phase III placebo-controlled trials involving patients receiving 5-FU failed to shown any protective benefits. [32].

Suspension of glutamine has been tried in different trials with inconclusive results. Huang et al. have conducted a pilot study in radiation-induced oral mucositis, and authors concluded that glutamine may significantly reduce the duration and severity of oral mucositis. However, the number of patients who received the active drug was only eight. In another study conducted by Jebb et al., which evaluated 5FU-induced and folinic acid–induced mucositis in 28 patients, it was concluded that there is no effect of oral glutamine supplementation.

The failure of oral glutamine to produce clinical benefits in these early trials was thought to be a result of the

unmodified agent's poor solubility, limited cell uptake, and overall chemical liability. A novel drug delivery system was developed to concentrate active glutamine near the epithelial cells in the at-risk oral mucosa. The vehicle for this system known as Aesgen 14 (AES-14) consist of ingredient classified by the FDA as "generally regarded as safe". The product is used 2 to 3 times per day as a mouth rinse and based on *in vitro* studies, is designed to increase delivery and bioactivity of active glutamine to target mucosa by 10-100 fold. Phase III clinical trials using AES-14 now have been completed, involving 326 woman who developed WHO grade 2 to 4 mucositis in the first screening cycle of the 3 planned cycle of anthracycline- based chemotherapy. In this randomized, double blind, crossover trials, the incidence of grade 2 to 4 mucositis in the first treatment cycle was 22 % less with AES-14 versus a placebo (p= .0261); analysis of the crossover data indicated that this mucoprotective effect appeared to carry over into subsequent treatment cycles The safety profile was comparable to that of a placebo [33]

2. CONCLUSION

Several studies have evaluated the benefit of oral or parenteral glutamine supplementation in cancer patients receiving chemotherapy and/or radiotherapy or after bone marrow transplant, with. L-glutamine is considerably reduce the duration and severity or oral mucosa during radiotherapy Many traditional treatments are ineffective. The basic principles of it is to relieve pain, prevent dehydration provide adequate nutrition and deal with any focus of infection such as stand the test of time approaches to the prevention of mucositis.

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REFERENCES

1. Knox JJ, Puodziunas AL, Feld R. Chemotherapy-induced oral mucositis. Prevention and management. Drugs Aging 2000;17(4): 257–267.
2. Woo SB, Sonis ST, Monopoli MM, Sonis AL. A longitudinal study of oral ulcerative mucositis in bone marrow transplant recipients. Cancer 1993;72(5): 1612–1617
3. Sonis ST, Elting LS, Keefe D, Peterson DE, Schubert M, Hauer- Jensen M, Bekele BN, Rader-Durlacher J, Donnelly JP, Rubenstein EB. Perspectives on cancer therapy-induced mucosal injury: pathogenesis, measurement, epidemiology, and consequences for patients. Cancer 2004;100 (Suppl 9):1995–2025
4. Lockhart PB, Sonis ST. Alterations in the oral mucosa caused by chemotherapeutic agents. A histologic study J Dermatol Surg Oncol 1981;7(12):1019–1025.
5. Schubert M., Sullivan K.,Truelove E., Head and neck complication of bone marrow transplantion, Development Oncology, 1991.
6. Eliá M. The inter-organ flux of substrates in fed and fasted man, as indicated by arterio-venous balance studies. Nutr res Rev 1991;4:3–31.
7. Medina MA. Glutamine and cancer. J Nutr 2001;131(9):2539S– 2542S
8. Skubitz KM, Anderson PM. Oral glutamine to prevent chemotherapy induced stomatitis: a pilot study. J Lab Clin Med 1996;127(2):223–228
9. Anderson PM, Schroeder G, Skubitz MD. Oral glutamine reduces the duration and severity of stomatitis after cytotoxic cancer chemotherapy. Cancer 1998;83(7):1433–1439
10. Anderson PM, Ramsay NK, Shu XO, Rydholm N, Rogosheske J, Nicklow R, Weisdorf DJ, Skubitz KM. Effect of low-dose oral glutamine on painful stomatitis during bone marrow transplantation. Bone Marrow Transplant 1998;22(4):339–344
11. Jebb SA, Osborne RJ, Maughan TS, Mohideen N, Mack P, Mort D, Shelley MD, Elia M. 5-Xuorouracil and folinic acid-induced mucositis: no eVect of oral glutamine supplementation. Br J Cancer 1994;70(4):732–735
12. Okuno SH, Woodhouse CO, Loprinzi CL, Sloan JA, LaVasseur BI, Clemens-Schutjer D, Swan D, Axvig C, Ebbert LP, Tirona MR, Michalak JC, Pierson N .Phase III controlled evaluation of glutamine for decreasing stomatitis in patients receiving Fluorouracil (5-FU)-based chemotherapy. Am J Clin Oncol 1999;22(3):258–261
13. Pytlík R, Benes P, Patorková M, Chocenská E, Gregora E, Procházka B, Kozák T. Standardized parenteral alanyl-glutamine dipeptide supplementation is not beneficial in autologous transplant patients: a randomized, double-blind, placebo controlled study. Bone Marrow Transplant 2002;30(12):953–961
14. Cerchietti LC, Navigante AH, Lutteral MA, Castro MA, Kirchuk R, Bonomi M, Calabar ME, Roth B, Negretti G, Sheinker B, Uchima P. Double-blinded, placebo-controlled trial on intravenous L-alanyl-L-glutamine in the incidence of oral mucositis following

chemoradiotherapy in patients with head-and-neck cancer Int J Radiat Oncol Biol Phys 2006;65(5):1330–1337

15. Lacey J, Wilmore D Is glutamine a conditionally essential amino acid? Nutr Rev 48(8):297–309 22. Neu J, DeMarco V, Li N (2002) Glutamine: clinical applications and mechanisms of action. Curr Opin Clin Nutr Metab Care 1990;5(1):69–75
16. Johnson AT, Kaufmann YC, Luo S, Todorova V, Klimberg VS. EVect of glutamine on glutathione, IGF-I, and TGF-_1. J Surg Res 2003;111: 222–228
17. Kubota A, Meguid M, Hitch D. Amino acid proWles correlate diagnostically with organ site in three kinds of malignant tumors. Cancer 1992;69(9): 2343–2348
18. Hong RW, Rounds JD, Helton WS, Robinson MK, Wilmore DW. Glutamine preserves liver glutathione after lethal hepatic injury. Ann Surg 1992;215(2): 114–119
19. Welbourne TC .Ammonia production and glutamine incorporation into glutathione in the functioning rat kidney. Can J Biochem 1979;57(3): 233–237
20. Welbourne TC, Dass PD. Function of renal gamma-glutamyltransferase: Significance of glutathione and glutamine interactions. Life Sci 1982;30(10): 793–801
21. Kandil HM, Argenzio RA, Chen W, Berschneider HM, Stiles AD, Westwick JK, Rippe RA, Brenner DA, Rhoads JM. L-glutamine and L-asparagine stimulate ODC activity and proliferation in a porcine jejunal enterocyte line. Am J physiol 1995;269: 591–599
22. Rhoads JM, Argenzio RA, Chen W, Rippe RA, Westwick JK, Cox AD, Berschneider HM, Brenner DA .L-glutamine stimulates intestinal cell proliferation and activates mitogen-activated protein kinases. Am J Physiol 1997;272: 943–953
23. Hong RW, Rounds JD, Helton WS, Robinson MK, Wilmore DW. Glutamine preserves liver glutathione after lethal hepatic injury. Ann Surg 1992;215(2): 114–119
24. Denno R, Rounds JD, Faris R, Holejko LB, Wilmore DW. Glutamine-enriched total parenteral nutrition enhances plasma glutathione in the resting state. J Surg Res 1996;61(1): 35–38
25. Yu JC, Jiang ZM, Li DM, Yang NF, M-X B . Alanyl-glutamine preserves hepatic glutathione storesafter 5-FU treatment. Clin Nutr 1996;15(5):261–265
26. Yu JC, Jiang ZM, Li DM . Glutamine: a precursor of glutathione and its eVect on liver. World J Gastroenterol 1999;5(2): 143–146.
27. Rennie M., Ahemed , A Khogli S. Lowl., Hundel.H., Effect o f oral glutamine on oral mucositis.,The Annals of Pharamacotherapy 1996, 36-39.
28. Sacks GS, Aimee B.Sacks, Solid and Semi-solid delivery formulation of L-glutamine for treating oral inflammation., US Patent Application Publication, US 2004/0265359 A1.)
29. Yen E, Stephen HA, Leung W, Wong CJ. influence of oral glutamine on radiation-induced oral mucositis in the radiotherapy of head and neck Int. J. Rad. Onco. 2000.
30. www. ClinicalTrials.gov. A service of National Institute of Health, Glutamine in treating mucositis caused by radiation therapy in patients with newly diagnosed cancer of the mouth or throat, January 25, 2008.
31. Klimberg VS, Pappas AA, Nwoedi E. Effect of supplemented dietary glutamine an methotrexate concentration in tumor Arch Surg 1992; 127: 1317-1320.
32. Okuro SH, Woodhouse CO, Loprinz C. Phase III controlled evaluation for decreasing stomatitis in patients receiving fluorouracil (5-FU) based chemotherapy Am J clin Oncol. 1999;22: 258-261.
33. Peterson DE, Petil RG. Phase III study : AES-14 in patients at risk for mucositis secondary to anthracycline based chemotherapy. J Clin Oncol 2004; 22(145): 8008.