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Mechanism and effects of Amino Acid (L-Glutamine) In Treatment of Oral Mucosal Injuries Induced By Radiotherapy and Chemotherapy

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ABSTRACT:
The present cures of various cancers comprise radiotherapy with or without cytotoxic substances. Disappointingly, these treatments can bring about surroundings and general impediment such as mucosal injuries or mucositis. These mucosal injuries can grounds a significantly affect quality of life in patients undergoing such treatment, by now anguish from psychosomatic collapse. 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. It is very difficult for clinician to choose from this incomprehensible array of treatment options. The endeavor of present review article was to appraise the competence of amino acid (L-glutamine) to cure buccal (oral) mucosal injuries provoked by chemo-radiotherapy in oncology. A variety of evaluation believed that amino acid (glutamine) administration restrain tumour, by reinstates the role of cytotoxic cells; progress protein transformation and assimilation along with; probably augment the worth of Oncological regimen.

Keywords: Oral Mucositis, L-Glutamine, Chemotherapy, Radiotherapy

INTRODUCTION

Oral mucositis is a repeated and dose-limiting consequence of chemotherapy. This state is related with uneasiness indications, falling patients' quality of life, and mounting financial overheads in addition to menace of infectivity and sepsis.[1] Around one half of individual's develop lesions of such severity as to necessitate alteration of their cancer treatment and/or parenteral analgesia. The occurrence is constantly high among patients undergoing conditioning therapy for bone marrow/peripheral blood progenitor cell transplantation, constant infusion therapy for breast and colon cancer, and treatment for tumors of the head and neck simultaneous chemotherapy and radiotherapy. Patients in the high-risk procedure, severe mucositis take place with an occurrence in surplus of 60%.[(2)]

Oral mucositis is linked with noteworthy morbidity typify by pain, odynodysphagia, dysgeusia, malnutrition, lowered immunity, cachexia, increased acute-phase proteins and hyperlipidaemia, lack of fluids and it also enhance the threat for systemic infections in immune-compromised patients.[(3, 11, 12)]

Glutamine is a non-essential branched-chain amino acid that turn out to be conditionally essential as soon as demand surpass supply throughout catabolic stress or stage of rapid growth.[4,5] Glutamine add up to 30–35% of the amino acid-based nitrogen in plasma plays an vital role in gluconeogenesis, and give out as a fuel for swiftly dividing and growing cells (e.g. enterocytes, lymphocytes and fibroblasts). [6,7,8,9,10]

Glutamine is also an originator of antioxidant glutathione. Thus, Glutamine up-regulates glutathione synthesis in stress, and stimulate heat shock proteins (e.g. HSP 27, 70 and 72), support in defending the gut and myocardium.[13]

Glutamate is altered into α-Ketoglutarate (TCA cycle) and heading to ATP formation chiefly obligatory for cellular growth and development, oxidation-reduction balance, as well as energy from metabolism. Purpose of this article is to appraise the validation for the application of enteral amino acid (L-Glutamine) in deterrence of oral mucosal injuries in person who takes cytotoxic drug along with/or radiotherapy.

ORAL MUCOSITIS: BRIEF REVIEW

Oral mucositis is an unavoidable barrier of cancer treatment for instance head and neck radiotherapy, chemotherapy and Hematopoietic Stem Cell Transplantation (HSCT), autologous or allogeneic, has an occurrence of 75%–99% and affecting over 40% of patients.[14,15,16]

Succession of mucositis entails five biological phase, unambiguously*:*

Initiation: Cover the primary injury in the order of succeeding to application of cytotoxic chemotherapy.

***Message generation*:** With reference to controlling of transcription factors comprise NFκB, MAPK, matrix metalloproteinases and subsequent commencement of cytokine and stress response genes.

Signaling and amplification: Produce proteins such as tumour necrosis factor, interleukin-1β and interleukin-6 which show the way to straight tissue spoil as well as present optimistic response to exaggerate the evolution.

Ulceration: Consequences in excruciating ulcers, bacterial admittance as well as an incursion of macrophages and additional inflammatory cells.

***Healing*:** This impulsively takes position upon annihilation of chemotherapy.[17]

The harshness depends on an array of factors, including the dose of medication, dose intermission, and the extent of treated tissue and the temperament of radiation exposure.[18,19]

The transcription factor is triggered reaction to chemotherapy and radiotherapy and is held responsible for the upregulation of up to 200 genes that shows mucosal integrity by acclerating clonogenic cell death, apoptosis and tissue damage across the entire mucosa, not restricted to the epithelium.[20] NF-jB activation ends in the production of pro-inflammatory cytokines, with tumour necrosis factor (TNF or TNF-a), interleukin-1b (IL-1b) and interleukin-6 (IL-6). [21, 22, 23]

The NF-jB's action comprises additional path intervention between neoplastic and normal cells ensuing in greater than before tissue harm in normal cell populations in contrast to neoplastic populations. Other biologically active proteins or pro-inflammatory mediators,

like cyclooxygenase-2 (COX-2) are up-regulated and start an inflammatory sequences of reactions leading to activation of matrix metalloproteinases whose presence bring out auxiliary tissue damage.[24] Tumour necrosis factor is competent to cause tissue damage {32} and possibly hastening and set off episode in the mucositis development. Tumour necrosis factor is chiefly expressed by macrophages, NK cells and T- lymphocytes. [25, 26]
The two receptors for TNF are expressed moreover on all cell types (TNF-R1) or just on immune or endothelial cells (TNF-R2).[26]

In fact IL-1b and TNF have been reported to have a synergistic effect, for example causing induction of endothelial adhesion molecules essential for the initial phases of the inflammatory response. [27]

Undoubtedly it is clear that different cytotoxic drugs stimulate diverse molecular pathways and, whilst the clinical outcomes may be analogous, the routes foremost to those outcomes may be immensely different. This has important implications for the opening out of targeted treatment for mucositis. Further categorization of the biological events taking place in the perspective of mucositis will unavoidably lead to enhanced treatment results and quality of life for patients undergoing cancer treatment.

MECHANISM AND EFFECT OF GLUTAMINE IN MUCOSAL INJURIES

Glutamine is a non-essential branched-chain amino acid that becomes conditionally essential when demand exceeds supply during catabolic stress or periods of rapid growth.[28,29] Glutamine contributes 30–35% of the amino acid-based nitrogen in plasma, plays an important role in gluconeogenesis, and serves as a fuel for rapidly dividing and growing cells (e.g. enterocytes and lymphocytes).[29,30,31,32] It contains two ammonia groups: glutamate and ammonia.[30] Glutamine transports ammonia in a non-toxic form, from the peripheral tissue to visceral organs, where it is excreted in the urine.[31]
Glutamine has protein formation effects go through Bone Marrow Transplantation patients who demonstrate after transplant body protein reductions.
Glutamine absorption in person with colon cancer is equivalent to uptake in person with healthy intestinal tissue, in addition food fortified with glutamine augment muscle glutamine in animal (rats) by 60%.[33, 34, 35] and diminish in methotrexate provoked adverse effects, with mucositis, and enhanced endurance is solicited. [36,37]
Amino acid (Glutamine) is the chief medium for distribution of nitrogen (ammonia) in a safer form. It is regarded as glutamine entrap.[38, 39, 40] The tumor producing human cell (breast) exhibits upside control of enzyme (glutamine synthetase) and mRNA in addition to it decrease in glutamine concentration (intracellular) on condition such as continual glutamine deficit.[41]
Glutamine may help decrease mucous membrane injury induced by radiation by altering the inflammatory response. Glutathione, a byproduct of glutamine metabolism protects against oxidant injury.[42,43] Glutathione act as contender to formation of prostaglandins (E2, mediator in inflammation). [44]
Studies demonstrate that glutamine or alanyl glutamine speed up mucosal renovation on or after 5-fluorouracil provoked oral mucositis by mounting glutathione supplies in mucosal tissue (hamster).[45]

Study explains that Glutamine considerably compact the frequency and deferred the commencement of score ≥3, decreased the demand for unexpected treatment discontinuation, and decrease the need of hospital stay. [46]

In an evaluating assessment, amino acid (L-Gln) appreciably decreases the period and harshness of oral mucosal injuries in person getting 50 (Gy/25) fraction of radiation. [47]

In study involve human, amino acid L-Gln in a career AES-14 that significantly boost its absorption, revealed to reduce score 2 or upper mucositis in person in receipt of cytotoxic drug.[48,49, 50]

Parenteral glutamine administration (>0.25-0.3g/kg/day) demonstrated the greatest benefit in hospitalized patients.[51]

Immune cells for instance lymphocytes and macrophages consume glutamine. In a study prevalence of bacterial infection in blood was lesser in which glutamine administered group in contrast with other group (control).[52,53,54,55]

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.[56,57] Second, previous studies have suggested that glutamine augments host defenses and may be important in glutathione synthesis thus decreasing the oxidative stress. [58,59,60,61]

ADVERSE EFFECTS OF ORAL GLUTAMINE

Some studies reviewed (12), In 1 retrospective study, rates of nausea were comparable between glutamine and control groups (grade 1, 32.1% vs 29.2%; grade 2, 19.6% vs 16.7%) during the 7 days prior to receiving radiation therapy. Another prospective study reported a similar occurrence of subjective adverse events between glutamine and control arms (nausea, 8.8% vs 8.3%; vomiting, 1.6% vs 1.9%; dry mouth, 5.2% vs 4.1%; anorexia, 0.7% vs 0.3%). Five other studies reported that no adverse events were observed, although methods for adverse event determinations were not clearly defined.[63,46,62]

CONCLUSION

Glutamine use is still a clinical and rationally attractive management approach. Adequate Glutamine administration, as part of nutrition therapy of cancer patients, is out of harm's way, when administered to the right patient for the correct reason. Glutamine supplementation may progress Quality of life by declining the incidence and/or severity of chemotherapy-associated mucositis. No published clinical guidelines or recommendations exist concerning the use of Glutamine supplementation in neonatal or pediatric patients. Inadequate proof exists to either recommend regular use of Glutamine in adults, or to provide guidance on Glutamine supplementation for prevention or diminution of severe mucositis. Glutamine depletion has been found to occur because of Glutamine consumption by lymphocytes and enterocytes in an enhanced metabolic condition. It not only modulates the immune system's role but also promotes faster healing, considerably decreasing the severity of mucositis/stomatitis induced by chemotherapy and radiation therapy. Glutamine may also boost the selectivity of antitumor drugs by sensitizing the tumor cells to the oncological

therapeutics while protective normal cells in healthy tissues.

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