

Chemotherapy-Induced Oral Mucositis: Can We Nip it in the Bud?

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Pediatric oncology has transformed in recent years. Diseases which were once considered incurable are now becoming curable with chemotherapy, immunotherapy, and radiation therapy. Chemotherapy undoubtedly is the main pillar for the treatment of childhood cancers, but it is associated with its own array of side-effects. Oral mucositis is one of them. It affects the quality of life adversely. So, now the focus is shifting from “just treating” to making the treatment “safer and more tolerable” for the children.

Chemotherapy-induced oral mucositis usually begins 5–7 days after the initiation of chemotherapy and lasts for 7–14 days. Basal epithelial layer of the oral mucosa has a rapid cellular turnover, so it is more susceptible to damage [1]. Chemotherapy causes the mucosal lining of the mouth to atrophy and break down, forming ulcers and erythematous patches causing burning sensation, pain and difficulty in eating, drinking, and speaking. In addition, the oral lesions weaken the mucosal barrier resulting in secondary local or systemic infections [1]. Reduced appetite leads to poor nutritional status as well. Chemotherapeutic agents that affect the DNA synthesis (S-phase), e.g., methotrexate, cytarabine, and 5-fluorouracil, have a high incidence of oral mucositis [1]. Various scales are used to define the severity of oral mucositis. The World Health Organization (WHO) Oral Toxicity Scale combines both objective and functional elements into a single score and is commonly used.

Mucositis poses an added financial burden due to the cost of associated supportive care including the use of total parenteral nutrition (TPN) in severe mucositis. Increased translocation of bacteria through damaged mucosal linings can lead to bacterial sepsis warranting hospitalization and administration of antibiotics which increases the treatment cost and morbidity. Also, if mucositis is prolonged, it becomes difficult to adhere to the intended schedule of

therapy leading to unwanted treatment delays. This calls for preventive steps for chemotherapy-induced oral mucositis. Good oral hygiene, ice-chip cryotherapy, non-medicated oral rinses like saline water or sodium bicarbonate rinses, antiseptic mouth washes like chlorhexidine and povidone-iodine, anti-inflammatory agents like benzydamine mouthwash, amino acid nutrients like glutamine, and keratinocyte growth factor like palifermin are the various modalities that have been explored for the prophylaxis of chemotherapy-induced mucositis.

Glutamine, a major dietary non-essential amino acid, has shown to assist in the healing of tissues damaged by chemotherapy or radiation [2]. It is an important nitrogen donor in intracellular metabolism and has trophic effects on the cells lining the gastrointestinal tract, immune cells and muscles [2]. The use of glutamine for managing cancer chemotherapy-induced mucositis dates back to 1980s with a few clinical trials conducted in the 1990s [3, 4]. In 1998, Skubitz and Anderson demonstrated the utility of oral glutamine in a randomized, double blind, crossover trial in adult patients receiving chemotherapy [3]. In their study, patients were either given glutamine or placebo to swish and swallow during and after chemotherapy and their paired data indicated significant amelioration of stomatitis associated with glutamine administration after chemotherapy. Since, then some studies have shown the efficacy of glutamine in chemotherapy-induced oral mucositis including a few in children [5–8]. Aquino, et al. in a double-blind randomized placebo-controlled trial evaluated oral glutamine in the prevention of mucositis in children undergoing hematopoietic stem cell transplantation and proclaimed that glutamine was safe and beneficial in reducing the severity of mucositis [5]. Widjaja, et al. showed significant difference with the use of oral glutamine in the prevention of methotrexate-induced oral mucositis in children with acute lymphoblastic leukemia (ALL) [6]. They also demonstrated that the glutamine group had a shorter treatment duration and thus the total cost incurred was two times less in glutamine group than the placebo group [6]. The Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology

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(MASCC/ISOO) published evidence-based clinical practice guidelines for oral mucositis which suggested that oral glutamine has a role for the prevention of oral mucositis in patients with head and neck cancer receiving radiotherapy or chemotherapy [9]. However, the panel recommends against the use of parenteral glutamine for the prevention of oral mucositis [9].

The present study by Sankaran, et al. has studied the efficacy of glutamine mouthwash in preventing methotrexate-induced mucositis in Indian children with ALL in a randomized cross-over trial, wherein children were randomized to receive either two consecutive courses of high dose methotrexate (HDMTX) with glutamine mouthwash plus standard oral hygiene protocol (SOHP), followed by two HDMTX courses with SOHP only; or vice-versa [10]. Glutamine suspension was administered twice daily by swish and swallow technique, starting one day before the course of HDMTX and continued up to 7 days or till mucositis persisted. Although, the overall incidence of mucositis was comparable in both groups, the glutamine group had a significantly lesser incidence of severe mucositis [3.1% vs. 44%; $P < 0.001$], shorter overall duration of mucositis [2 (0, 3) days vs 5 (3, 5) days, $P < 0.001$] and lower median pain scores [$P < 0.001$] [10]. The study provides objective evidence to emphasize that swish and swallow glutamine mouthwash alleviates severe mucositis associated with chemotherapy in children and accelerates recovery. This not only improves the quality of life but also ensures adherence to chemotherapy protocols. More studies in Indian children can cement the role of glutamine in the management of chemotherapy-induced oral mucositis.

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