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Phase II multicenter trial of Caphosol for the reduction of mucositis in patients receiving radiation therapy for head and neck cancer

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SUMMARY

Purpose: We conducted a phase II multicenter study evaluating Caphosol in patients receiving head and neck radiation (H/N RT) +/− chemotherapy or biologic sensitizer.
Materials/Methods: The primary endpoint of the study tested the rate of functional mucositis (WHO grade > or equal to 2) with the hypothesis that <75% of patients would develop > or equal to 2 mucositis with Caphosol compared with a historical rate of >90%. New methods were applied with higher than historic rigor. 5 Institutions were included in this study: Moffitt Cancer Center (MCC), MD Anderson Cancer Center (MDACC), Duke University Cancer Center (DUCC), University of Florida (UF) and Temple University Cancer Center (TUCC). Caphosol was taken by patients at least 4 times a day and up to 10 times per day commencing with day 1 of RT and for a total duration of 8 weeks after completion of RT. Detailed questionnaires were completed weekly by patients and a unique algorithm was used to generate the WHO grade of mucositis.
Results: 98 Patients were enrolled in the study. 59/98 (60%) patients were evaluable for the primary endpoint giving us 80% power. All evaluable patients experienced WHO grade > or equal to 2 mucositis and the trial failed to reject the null hypothesis. > or equal to 2 mucositis rates at weeks 2, 4, 6, 11 and 15 were as follows: 45%, 90%, 98%, 71%, 50%.
Conclusion: We were unable to demonstrate that Caphosol significantly reduced WHO grade 2 or higher mucositis below a 90% historic rate. We are not surprised with this finding given our rigorous methodology in grading.

Introduction

Radiation therapy with systemic therapy is the standard of care in the treatment of locally advanced squamous cell carcinoma of the head and neck [1,2]. While clinical outcomes may be favorable, acute treatment related toxicity may be considerable [3].

Mucositis is a debilitating complication of head and neck cancer radiation therapy and chemotherapy that is characterized by inflammation of the mucous membranes, erythema, ulceration, and pseudomembrane formation [4]. Mucositis can cause pain and dysphagia which is further complicated by the frequent association of xerostomia and altered taste. Mucositis may lead to anorexia, weight loss, weakness and contribute to depression. Furthermore severe inflammation and ulceration of the mucosa predisposes patients to both oral and systemic infections. Difficulties of pain management and nutrition can be exacerbated by side effects of opioid use and the need for parenteral nutrition. The incidence of mucositis is estimated at approximately 400,000 patients per year with about 97% of patients receiving head and neck radiation therapy experiencing this side effect [5,6].

Caphosol is an electrolyte solution, designed in part to replace the normal ionic pH balance in the oral cavity and may be useful in the prevention and treatment of mucositis in cancer patients

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[7,8]. When mixed together the calcium solution and the phosphate solution form a stable supersaturated solution with a composition resembling that of natural saliva. It has been postulated that Caphosol's high ionic content plays a role in mediating the inflammatory process, coagulation cascade, and in assisting with tissue repair by diffusing ions into the intercellular spaces in the epithelium thus permeating the mucosal lesion [9]. Calcium is known to play a crucial role in several aspects of the inflammatory process including effecting leukocyte chemotaxis, modulation of adhesion molecules, and the elaboration of arachiodonic metabolites, and phosphate is a central compound involved in cellular and tissue repair.

While its effectiveness has been documented in patients with hematological malignancies undergoing stem cell transplant, there have been no prospective evaluations in radiotherapy-related mucositis of the head and neck region [9]. The purpose of this study was to estimate the effect of Caphosol on the incidence of oral mucositis in patients receiving radiation therapy with or without systemic therapy for the treatment of head and neck cancer and to correlate the extent of mucosal injury and components of WHO mucositis data with clinical outcomes (including oral intake, swallowing function, and pain), and patient preference.

Materials and methods

The study was conducted at 5 centers in North America including Moffitt Cancer Center (MCC) (serving as the coordinating data center), MD Anderson Cancer Center (MDACC), Duke University Cancer Center (DUCC), University of Florida (UF) and Temple University Cancer Center (TUCC). After institutional review board approval at each participating center, patients provided informed written consent. This process took place in accordance with the Health Insurance Portability and Accountability Act, Good Clinical Practices, and with local and legal requirements. Data monitoring at the sites was performed by MCC.

Patients with newly diagnosed squamous cell carcinoma of the head and neck including the oral cavity, oropharynx, nasopharynx, hypopharynx and larynx were eligible including postoperative cases. Eligible patients were planned to receive at least 60 Gy or greater to at least one of 9 pre-defined anatomic mucosal subsites seen on direct view of the oral cavity and oropharynx (Fig. 1). Conventional fractionation, accelerated fraction and hyperfractionation radiation therapy schedules were permissible. 2D, 3D- conformal and intensity modulated radiotherapy (IMRT) techniques were allowed. Major radiation protocol violations included treatment breaks greater than 2 weeks and receiving less than 80% of the prescribed dose. Concurrent platinum based chemotherapy or cetuximab was permissible. Systemic therapy consisted of cisplatin 100 mg/m^2 every 3 weeks, cisplatin 30–40 mg/m^2 weekly, Carboplatin 2 AUC/week or cetuximab 400 mg/m^2 loading dose 7 days before radiation plus 250 mg/m^2/week for 6–7 weeks. Patients were not eligible if they demonstrated mucosal ulceration at baseline unless the surgical site was at least 95% healed, if they demonstrated active infections of the oral cavity or oropharynx other than candidiasis, if they had received induction chemotherapy, or if they had significant comorbidities precluding adequate compliance.

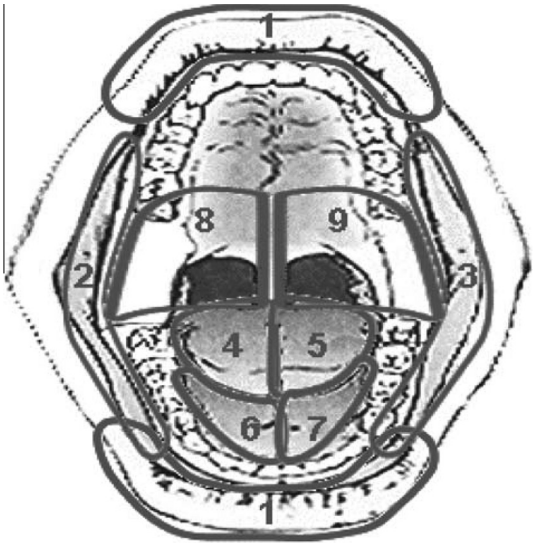

Fig. 1. 9 Zones evaluated by investigators for ulceration.

The study was an open label single arm trial. Caphosol use with radiation therapy with or without cisplatin or cetuximab commenced day #1 of radiation and continued for 8 weeks after the completion of therapy. Patients took Caphosol by mixing the calcium and phosphate solutions together, rinsing for 1 min with a half portion, spitting and then repeating with the remainder at least 4 times per day and up to 10 times per day. Patients were assessed weekly during radiation therapy, 4 weeks and 8 weeks after therapy. Standard of care topical anesthetics including "Magic Mouthwash" consisting of combinations of lidocaine, diphenhydramine, Maalox, and/or nystatin was permissible and the management of candidiasis was left to the discretion of the treating physician. Other systemic or topical agents for the treatment of mucositis were not allowed.

Investigators developed new structured patient evaluation and data capture methods for this trial. These included mandatory completion of a web-based study specific mucositis training module for each investigator, specific guidance on assignment of food type, oral feedings, and a unique automated algorithm for assigning details. The algorithm standardized WHO grade I to IV mucositis based on the presence of pain, mode of nutrition, form of nutrition and presence of ulceration.

Patients completed a patient satisfaction tool (PST) that included mouth and throat pain, swallowing, eating and overall symptoms. Grading was by improvement, no change or worsening symptoms. Adverse events monitoring took place as per Common Terminology Criteria version 3.0. Severe adverse events (SAEs) attributable to Caphosol were defined as those resulting in death, life threatening, requiring hospitalization, requiring intervention to prevent permanent impairment, or as determined by the principal investigator.

Statistical methods

The evaluable patients for the primary analysis were defined as those who used at least 80% of the study agent at a minimum of 4 doses per day without major radiation protocol violations. The primary end point of this study was the development of functional mucositis WHO grade $\geqslant 2$. We hypothesized that less than 75% of patients would develop grade 2 or greater mucositis with Caphosol compared with a historical rate of greater than 90% [3]. Using 80% power and a two-sided significance level of 0.05 it was determined that 48 valuable patients would be needed. The comparison was performed using an exact test for the binomial distribution. The WHO grade was summarized at each time point.

Results

Patients

The study was opened on April 9th 2009 and the last patient was enrolled on April 9th 2010. A total of 98 patients participated.