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CLINICAL INVESTIGATION **Head and Neck**

PROTECTION OF SALIVARY FUNCTION BY CONCOMITANT PILOCARPINE DURING RADIOTHERAPY: A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY

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Purpose: To investigate the effect of concomitant administration of pilocarpine during radiotherapy for head-and-neck squamous cell carcinoma (HNSCC) on postradiotherapy xerostomia.

Methods and Materials: A prospective, double blind, placebo-controlled randomized trial including 170 patients with HNSCC was executed to study the protective effect of pilocarpine on radiotherapy-induced parotid gland dysfunction. The primary objective endpoint was parotid flow rate complication probability (PFCP) scored 6 weeks, 6 months, and 12 months after radiotherapy. Secondary endpoints included Late Effects of Normal Tissue/Somatic Objective Management Analytic scale (LENT SOMA) and patient-rated xerostomia scores. For all parotid glands, dose–volume histograms were assessed because the dose distribution in the parotid glands is considered the most important prognostic factor with regard to radiation-induced salivary dysfunction.

Results: Although no significant differences in PFCP were found for the two treatments arms, a significant ($p = 0.03$) reduced loss of parotid flow 1 year after radiotherapy was observed in those patients who received pilocarpine and a mean parotid dose above 40 Gy. The LENT SOMA and patient-rated xerostomia scores showed similar trends toward less dryness-related complaints for the pilocarpine group.

Conclusions: Concomitant administration of pilocarpine during radiotherapy did not improve the PFCP or LENT SOMA and patient-rated xerostomia scores. In a subgroup of patients with a mean dose above 40 Gy, pilocarpine administration resulted in sparing of parotid gland function. Therefore, pilocarpine could be provided to patients in whom sufficient sparing of the parotid is not achievable. © 2008 Elsevier Inc.

Radiation-induced xerostomia, Pilocarpine, Dose–volume response, Randomized study.

INTRODUCTION

Xerostomia is a common, disturbing side effect among patients treated with radiotherapy for head-and-neck cancer, leading to considerable morbidity, including severe oral discomfort, problems with speaking, dysphagia, and an increased incidence of caries and mucosal infections (1). Although salivary gland tissue is a well-differentiated tissue and theoretically should be relatively radioresistant, studies have shown a rapid decline in parotid and submandibular/sublingual salivary flow, even after low doses of radiotherapy (2). In human, it has been reported that the TD_{50} (*i.e.*, the dose to the whole organ leading to a complication probability of 50%) for parotid glands varies from 28.4 Gy (3) to 31 Gy at 6 weeks, increasing to 39 Gy at 1 year after completion of radiotherapy (4). Although new radiation techniques enabled significant sparing of the parotid glands, the amount of normal salivary gland tissue irradiated may still be substantial and result in clinically relevant radiation-induced xerostomia (5–8). Therefore, protection against radiation-induced salivary gland damage may further improve the therapeutic gain.

Promising results on reducing radiation injury to salivary gland tissue and thus on preservation of gland function have been claimed by concomitant administration of pilocarpine during radiotherapy. Two nonrandomized (9, 10) and two randomized trials (11, 12) indicated that the risk of radiation-induced xerostomia was reduced when pilocarpine was given during radiotherapy. However, no such beneficial effect was observed in six other randomized clinical trials (13–18). How can these conflicting results be explained? From animal experiments, it is known that the protective

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effects of prophylactic pilocarpine treatment is dependent on the irradiation dose and irradiated volume of the salivary gland (19). In the various clinical trials, however, details on dose distribution and dose–volume histograms were generally lacking, and patients were treated with standard techniques to doses of 50 Gy or more. Detailed information on the dose distribution in the salivary gland is essential because it is the most important prognostic factor for developing salivary dysfunction and therefore potentially the most important confounder. For this reason, it remains difficult to draw definitive conclusions from the results published to date.

Therefore, the objective of this prospective, randomized, placebo-controlled clinical trial was to investigate the effect of concomitant administration of pilocarpine during radiotherapy for head-and-neck squamous cell carcinoma (HNSCC) on postradiotherapy xerostomia. In addition, the observed effects were related to the dose distribution in the parotid glands.

METHODS AND MATERIALS

Eligibility criteria

To be eligible for this study, patients had to have a biopsy-confirmed HNSCC. All patients were treated at the departments of Radiation Oncology of the University Medical Center Utrecht and the University Medical Center Groningen. Eligible patients received either primary or postoperative radiotherapy. The initial 5% (wt/vol) citric acid–stimulated parotid salivary flow had to be >0.1 mL/min. Excluded were patients who underwent previous irradiation and/or previous or concurrent chemotherapy, patients with salivary gland tumors, patients with severe cardiovascular disease or chronic obstructive pulmonary disease, patients using cardiac medication like β-blockers (contra-indication for the use of pilocarpine), or other medication influencing salivary gland function. Pregnant women were also excluded. The study was approved by the local ethics committees of the participating centers, and written informed consent was obtained from all patients.

Study design

All patients included received at least 40 Gy to a part of both parotid glands. This threshold dose was chosen at that time because it was considered a high enough dose to cause definitive damage to the parotid glands. The volume of parotid tissue included in the radiation portals varied, depending on the primary tumor site. To ensure an equal distribution between patients receiving placebo and pilocarpine, patients were stratified into three groups on the basis of the expected irradiated volume of the parotid glands. Both submandibular glands, if not removed as part of a cervical lymph node dissection, always were irradiated to a dose of ≥40 Gy. The three groups had an expected irradiated volume of the parotid gland of 25%–45%, 46%–75%, and >75%, respectively. These three volume groups were arbitrarily chosen because we wanted to be sure that the whole range of irradiated volumes above the tolerance dose would be included in the study. Patients with an expected irradiated parotid volume <25% were excluded from this study because these glands were expected to exhibit an almost normal function after radiotherapy. Planning CT scans were made in all patients for treatment planning and for delineation of organs at risk, including the spinal cord and the major salivary glands.

All patients were randomly assigned to receive radiotherapy plus pilocarpine (5-mg tablets, four times per day) vs. radiotherapy plus placebo (similar tablets, four times per day). Pilocarpine or placebo administration was started 2 days before the start of radiotherapy and stopped 14 days after completion of radiotherapy.

Radiotherapy

Radiotherapy was delivered using megavoltage equipment (6-MV linear accelerator). The clinical target volume of the initial field encompassed the primary tumor site with a 1.5-cm margin, the neck node levels in which pathologic nodes were found, and the elective nodal areas on both sides. The clinical target volume of the boost included the primary tumor site plus a 1.0-cm margin and the nodal area's tumor-positive lymph nodes. For the planning target volumes (PTV), an additional 0.5 cm was applied in all directions. Treatment was given with a conventional fractionation schedule. The initial PTV was treated with daily fractions of 2 Gy to a total dose of 46 Gy. In case of primary radiotherapy, the PTV of the boost was irradiated to a total dose of 70 Gy with a dose per fraction of 2 Gy. In case of postoperative radiotherapy, the PTV of the boost was irradiated to a total dose of 60–64 Gy, depending on surgical margins and the presence of lymph node metastases with extranodal spread.

Assessment of salivary secretion

Assessment of parotid salivary flow was performed by four experienced investigators two times before the start of radiotherapy (to estimate the baseline value) and 6 weeks, 6 months, and 12 months after completion of radiotherapy. Using Carlson-Crittenden cups, saliva from the right and the left parotid gland was simultaneously collected under standardized conditions for 10 min (20). At the same time saliva from the remaining salivary glands (predominantly submandibular/sublingual saliva) was collected from the floor of the mouth by gentle suction with a syringe. Salivary flow was stimulated with 5% (wt/vol) citric acid, applied with a micropipette (50 μL) to the lateral border of the tongue at 60-s intervals. In addition the latent period was assessed, which was defined as the time elapsed between the start of saliva collection (first administration of citric acid) and start of saliva output (first drop of saliva originating from the orifices of the parotid glands). The collected saliva samples were weighted to estimate the volume (in milliliters) assuming the specific gravity of saliva to be 1.0 g/cm^3. The salivary flow rate (in milliliters per minute) was calculated by the formula: flow rate = mL of saliva/(10 min – latent period).

Assessment of subjective complaints

At the same time points at which saliva was collected, patients were asked to complete a validated head-and-neck symptom questionnaire (12 questions) containing domains on xerostomia, eating, and swallowing complaints. The questions were scored on a 5-point Likert scale and are also used in our clinic by oral surgeons for patients with Sjögren's syndrome. In addition, the Late Effects of Normal Tissue/Somatic Objective Management Analytic (LENT SOMA) morbidity scoring system (21) was completed.

Statistics

The primary endpoint was parotid flow rate complication probability (PFCP), defined as a reduction in flow rate to <25% reference to the flow rate at baseline (19). A PFCP incidence of 60% in the placebo group and of 35% in the pilocarpine group was assumed. To detect this difference, a total number of 162 patients was needed (power 90%, two-tailed $\alpha = 0.05$). Taking into account a dropout