Prospective Single-Arm Study of Radioprotection by Amifostine in High Dose Radioactive Iodine Therapy for Thyroid Cancer

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ABSTRACT

Purpose: Xerostomia, sialoadenitis, taste dysfunction and nausea are well known toxicities following high dose radioactive iodine (RAI) treatment for well-differentiated thyroid cancer. This prospective study sought to determine the incidence rates for RAI adverse effects and to determine, whether the radioprotector, amifostine could decrease the duration of the adverse effects in single treatment patients.

Materials and methods: Patients with differentiated thyroid cancer received 150 mCi RAI after total thyroidectomy. All patients were pretreated with 1 mg granisetron and 4 mg dexamethasone. Patients in the amifostine arm (n = 27) were prospectively enrolled and received 500 mg amifostine subcutaneously. Adverse effects were scored based on the CTCAE at 1 month, 6 months, and yearly intervals using a physician administered questionnaire. The results were compared with a retrospective no amifostine cohort (n = 22) for whom data was collected with the identical questionnaire.

Results: The overall incidence of xerostomia, sialoadenitis, taste dysfunction and nausea in the treatment group was 26, 22, 52 and 26% respectively. Only grades 1 and 2 adverse effects were observed. The mean duration (days) of xerostomia (control vs treatment)—37.3 vs 21.9 (F test, p = 0.016), taste dysfunction—45.5 vs 23.5 (F test, p = 0.001), sialadenitis—16.8 vs 7.5 and nausea—18.7 vs 5.1.

Conclusion: In patients treated once with high dose RAI, who develop xerostomia, sialoadenitis, taste dysfunction, and/or nausea, the duration of symptoms appears to be reduced by pretreatment with 500 mg of subcutaneous amifostine without significant treatment related adverse effects.

Keywords: Thyroid cancer, Radioprotection, Amifostine, Radioactive iodine, Prospective.


Source of support: Nil

Conflict of interest: None declared

INTRODUCTION

Over 25,000 cases of thyroid carcinoma were diagnosed in 2005 and about 75% were well-differentiated carcinomas.1 The age-adjusted incidence in women has increased 4.3% per year from 1992 though 2001, the fastest rise among malignancies tracked by SEER (surveillance epidemiology and end results).2 Differentiated thyroid cancer affects women 2.5 times the rate in men and most commonly presents in the fourth and fifth decades of life.

In our institution, total thyroidectomy followed by high dose 131-I RAI (radioactive iodine) remnant ablation is the standard treatment for patients with differentiated thyroid cancer.3-8 Accumulation of RAI in the salivary glands9-11 and the gastrointestinal tract12 results in a high incidence of xerostomia, sialoadenitis, taste dysfunction and nausea. Moreover, since over one-third of patients eventually require more than one RAI administration and the adverse effects increase with accumulated dose, the potential for developing long-term effects is a real danger. These adverse effects are known to cause difficulties with mastication, swallowing, speech, oral health and a reduction in quality of life.13,14

A European quantitative double-blind, placebo-controlled randomized trial has shown that the radioprotector, amifostine (Ethylol, MedImmune Oncology, Inc., Gaithersburg, MD), reduced parenchymal damage in salivary glands caused by high dose RAI.15 Additionally, a well-established literature documents the efficacy of amifostine for salivary gland protection in head and neck cancer irradiation.16-21

We conducted a prospective single arm study to determine the incidence of xerostomia, sialoadenitis, taste dysfunction and nausea as well as whether the radioprotector amifostine could decrease the duration of these adverse effects in patients treated with RAI one time.

MATERIALS AND METHODS

In our institution, patients with well-differentiated thyroid cancer receive 150 mCi RAI after total thyroidectomy for eradication of the thyroid remnant and any remaining cancer. Additionally, patients undergo whole body RAI scanning to access for metastatic disease and proper biodistribution 48 hours and 7 days post-RAI administration.

This was a prospective, nonrandomized, open-label study. Eligibility included age ≥16 years, initial systolic blood pressure >80 mm Hg (>100 mm Hg in patients ≥50 years), patients scheduled to receive a RAI treatment following total thyroidectomy for localized or metastatic well-differentiated thyroid carcinoma and absence of contraindications to amifostine. The study was conducted after approval was granted by the internal review board.
All patients were pretreated with 1mg granisetron and 4 mg dexamethasone 1 hour before receiving RAI to prevent RAI induced nausea. Patients in the amifostine arm (n = 27) were prospectively enrolled and received 500 mg amifostine subcutaneously (250 mg in each lateral deltoid) 15 to 30 minutes before RAI treatment. Amifostine was provided to patients enrolled in the study by MedImmune Oncology, Inc. All patients were instructed to maintain salivary gland stimulation to decrease impairment of salivary gland function (hard candies), to utilize prune juice to keep the bowels active and to maintain a high fluid intake so as to reduce the local collection of radioisotope in the bowel or bladder. All patients were dosed in an outpatient setting in accordance with guidelines of the US Nuclear Regulatory Commission (www.nrc.gov). Adverse effects were scored based on the National Institutes of Health Common Terminology Criteria (v3.0) for adverse events at 1 month, 6 months and yearly intervals using a physician administered questionnaire. Acute events were defined as those present for ≤6 months and chronic events for >6 months post-treatment. The results were compared with a retrospective no amifostine cohort (n = 22) for whom data was collected with the identical questionnaire. The difference in means of symptom duration between groups was based on the t-test and the variance of side effect duration between the two groups was examined with the F test to the 95% confidence interval. The software package used for statistical analysis was GraphPad Prism 3.03, San Diego, CA.

RESULTS

Twenty-seven patients were prospectively enrolled in the amifostine treatment arm. These patients were compared to 22 historical controls. The two groups were well balanced with regard to baseline characteristics (Table 1). The duration of follow-up in the control and treatment arms was 27.9 and 6.4 months (mean) and 23.4 and 7.9 months (median) respectively. Only grades 1 and 2 RAI induced toxicities were observed. The incidence of grades 1 or 2 xerostomia, sialoadenitis, taste dysfunction and nausea in the control and treatment groups are presented in Table 2. The mean duration of RAI induced toxicities after high dose RAI administration for control and treatment groups is shown in Table 3.

The mean duration of xerostomia (control vs treatment) was 37.3 vs 21.9 days (F test, p = 0.016). The mean duration of taste dysfunction was 45.5 vs 23.5 days (F test, p = 0.001). The mean duration of sialoadenitis was 16.8 vs 7.5 days. The mean duration of nausea was 18.7 vs 5.1 days. The variance in symptom duration was statistically decreased for xerostomia and taste dysfunction while a strong trend existed for sialoadenitis and nausea (Fig. 1). The only documented adverse effect to single dose amifostine was injection site rash (grade 1 only) which developed in 5/27 (18.5%) and resolved spontaneously by 2 weeks.

DISCUSSION

The physical half-life of RAI is 8 days but the biological half-life is largely dependent on the presence of thyroid tissue. Since RAI is administered after thyroidectomy, the biological half-life of RAI is expected to be short, excreted in the kidneys within several hours. There are cases of heavy tumor burden in which the biologic half-life is longer.

Amifostine (WR-2721) is an organic thiophosphate prodrug that rapidly (T1/2 < 1 minute) distributes throughout the plasma compartment. There it is quickly dephosphorylated by alkaline phosphatase to the active free thiol

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SEM: Standard error of the mean; d: days
Amifostine is approved by the FDA for administration intravenously. Recently, investigators have shown that subcutaneous administration has equivalent activity with improved tolerability.36-39

A double-blind, placebo-controlled randomized trial using quantitative salivary gland scintigraphy has shown that amifostine pretreatment reduces both acute and chronic xerostomia in patients treated with high dose RAI.15

The current study examined whether amifostine could reduce the duration of xerostomia, sialoadenitis, taste dysfunction, and/or nausea subsequent to a 150 mCi therapeutic dose of RAI in the postoperative treatment of well-differentiated thyroid cancer. This report evaluates patients treated with RAI one time in order to identify baseline adverse effect incidence rates and to assess for the efficacy of amifostine without the confounding factors associated with multiple RAI doses.

Fig. 1: Duration of toxicities after high dose RAI treatment

Salivary glands concentrate iodine 30 to 40 times the plasma level and have a dose dependent reduction in function following RAI.9,10 Xerostomia and sialoadenitis historically have been reported to occur in approximately 10% of patients who receive RAI therapy and most frequently in patients receiving multiple treatments.9,40,41

More recently, our group reported acute xerostomia in 21% and acute sialoadenitis in 16%.42 Chronic xerostomia occurred in 35% of patients receiving multiple treatments of RAI with this figure reduced to 9% after amifostine subcutaneous pretreatment.42 The current study prospectively evaluated the incidence of xerostomia and sialoadenitis in the treatment arm and found the incidence of each is approximately 25% (Table 2). When compared to a retrospective historical control from our department, amifostine subcutaneous pretreatment resulted in a statistically significant reduction in duration of xerostomia and a trend for a reduction in sialoadenitis (Fig. 1).

Taste dysfunction historically has been reported in up to 48% of patients treated with 150 to 200 mCi of RAI.43 Our prospective results indicate a comparable incidence rate of 52%. The duration of taste dysfunction was significantly reduced with subcutaneous amifostine pretreatment (see Fig. 1).

Nausea has been reported in 50 to 67% of patients treated with high dose RAI40,44 due to accumulation of RAI in the gastrointestinal tract.12 The current study revealed a 26% incidence of nausea which was not different from the non-amifostine arm. This indicates that subcutaneous pretreatment with single dose amifostine does not result in amifostine induced nausea—a well known side effect in daily amifostine administration protocols. Interestingly, amifostine pretreatment resulted in a strong trend (p = 0.063) for the decrease in the duration of nausea (see Fig. 1). This supports the theory that amifostine protects the gastrointestinal tract from RAI induced nausea.

A recent review45 on the use of RAI supported the use of larger ablation doses which is known to be more effective in terms of complete ablation of remnant thyroid. The dose between 100 to 150 mCi is standard practice for high-risk disease. Dose of mCi have been tried with disappointing results resulting and ablation is achieved only in 60% of cases. Complete ablation is well known to reduce relapse rates which can only be achieved with higher doses.

CONCLUSION

This single arm prospective study confirmed the high incidence rates of xerostomia (26%), sialoadenitis (22%), taste dysfunction (52%) and nausea (26%) after single high dose RAI administration for the postoperative treatment of well-differentiated thyroid cancer. There were no cases of
chronic adverse effects from single dose RAI. We have shown that subcutaneous pretreatment with amifostine decreases the duration of these RAI induced side effects without significant treatment related adverse effects. Pretreatment with subcutaneous amifostine can be easily incorporated into a clinical practice and may decrease or prevent potentially debilitating symptoms in an otherwise young and healthy patient population. We however caution that the routine use of amifostine is not recommended based on this study. Larger prospective studies should answer this important question. We are analyzing data from patients treated with multiple doses of RAI to determine, whether amifostine can prevent chronic RAI-induced toxicities.

DISCLOSURE
This study was conducted in the Department of Radiation Oncology at Sentara Norfolk General Hospital, a department of the Eastern Virginia Medical School. MedImmune Oncology, Inc. had no rights to oversee or review the results of the study.

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REFERENCES


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