Effect of Amifostine to prevent Radiotherapy-Induced Acute and Late Toxicity in Head and Neck Cancer Patients Who had Normal or Mild Impaired Salivary Gland Function

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Background: *Amifostine has a potential role for salivary gland protection in head and neck cancer patients who had radiotherapy.*
Material and Method: *Sixty-seven head and neck cancer patients were randomized to receive radiotherapy or radiotherapy plus Amifostine. The efficacy of the treatment was determined by a questionnaire evaluating dryness of mouth and the oral comfort, the RTOG/EORTC acute/late radiation morbidity scoring criteria, collection of the whole saliva and the 99mTc-pertecnetate scintigraphy of the salivary glands.*
Results: *Amifostine significantly reduced the mean questionnaire scores from 6.49 to 3.73, the incidence of grade ≥ 2 mucositis from 75% to 36% and acute xerostomia from 82% to 39%. The salivary gland function returned to normal at a rate of 36.3% in the Amifostine group versus 9.1% in the control group.*
Conclusion: *Amifostine is effective in reducing the incidence and severity of acute mucositis, acute and late xerostomia in head and neck cancer patients.*

Keywords: *Head and neck cancer, Radiotherapy, Amifostine, Mucositis, Xerostomia*

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Squamous cell carcinoma of the head and neck is a common cancer in Thailand. Radiotherapy should be considered for treating early stages of the disease to preserve organ function. For locally advanced disease, the combination of surgery and radiotherapy improve both the local control and the overall survival rate. Depending on the total radiation dose and the percentage of the salivary gland in the treatment field, xerostomia is likely to be the major side effect of radiotherapy that may affect the clinical outcome and compromise the patient's quality of life.

The most effective intervention for xerostomia is its prevention by treatment planning and beam arrangement designed to spare as much of the salivary glands as possible. The percentage of gland irradiated was a major determinant of the degree of salivary gland dysfunction, especially when this involved the parotids. About 60-65% of total saliva is produced by the parotid glands, which are purely serous, while 20-30% is produced by submandibular glands and the 2-5% produced by sublingual glands, which are mixed serous and mucous. The minor salivary glands throughout the oral cavity and pharynx contain a predominantly mucous component[1].

The radiation treatment of head and neck cancer mostly includes the salivary glands. The parotids appeared more radiosensitive than the submandibular glands, but three months after complete radiation treatment both glands were similarly impaired and remained impaired for up to six months. The stimulation response ratio was significantly decreased when 75-100% of the parotid gland tissue was irradiated compared to when 25-50% was treated[2]. The secretion function of parotid glands can recover after a total dose less than 52 Gy, beginning two months after radiation treatment with continuous improvement up to 18 months. Following doses of more than 64 Gy, the parotid function became irreversible and the dryness was severe and persistent[3].

In most conventional radiation treatment for head and neck cancer, parotid glands cannot be avoided or spared with a dose less than 50 Gy. Most of the patients had permanent xerostomia. The treatment of xerostomia used a saliva substitute ("artificial saliva") and salivary gland stimulants. However, these treatments require functional salivary gland parenchyma to be effective.

Use of Amifostine (WR 2721) as the radioprotective agent is another way to protect the salivary gland. The ability of its thiol-containing components to protect against normal tissue damage from radiation has been recognized for over 40 years. When Amifostine is administrated intravenously, it rapidly clears from plasma in less than ten minutes. The drug is taken up in the salivary glands and converted into active protective thiol (WR 1065) that acts as an oxygen-free radical scavenger. The Amifostine has been approved by the United States' Food and Drug Administration for reducing xerostomia in patients undergoing post operative radiation treatment for head and neck cancer where the radiation treatment area includes a substantial portion of the parotid glands. Many studies have shown its benefit in protecting salivary gland function and improving the quality of life of the patients after the treatment. It was not found to protect against tumors[4,5]. The major side effects of Amifostine are nausea/vomiting and transient hypotension. The other acute Amifostine related toxicity is the allergic skin reaction, which is observed in clinical trials or from clinician's reports[6,7].

In this multi-centered, open label, prospective, randomized study, the authors decided to test whether Amifostine has a potential role for salivary gland protection in Thai head and neck cancer patients who had received radiotherapy. The authors also tried to determine by the 99mTc-pertecnetate scintigraphy when the parotid glands had recovered.

Material and Method

Patients with newly diagnosed stage T1-3 or post operativeT4, N 0-1, M0 squamous cell carcinoma of head and neck cancer (oral cavity, oropharynx, hypopharynx, and nasopharynx) and who had $\geq$ 70% of both parotid glands within the radiation field were randomized to receive radiotherapy or radiotherapy plus Amifostine. The selected patients must not have previously had cancer or cancer treatment in another part of the body. The selected patients were required to be between 18-70 years of age, have Eastern Cooperative Oncology Group (ECOG) performance status $\geq$ 2 and adequate bone marrow function (Hemoglobin > 10 mg%, Leucocyte > 4000/mm^3, Granulocyte > 1500/mm^3, Platelet > 100000/mm^3), liver function (Bilirubin < 2.0 mg%, SGOT, SGPT, Alkaline phosphatase in normal range), and renal functions (Creatinine < 1.5 mg/ml). All of them should have a life expectancy of more than one year and be able to comply with a follow-up schedule. All the screening tests, examinations, and procedures were completed within 14 days before the start of treatment.

For radiotherapy in both groups, the authors used the Megavoltage equipment (Linear accelerator

or Cobalt-60). The patients received the definite radiotherapy 66-70 Gy or post operative radiotherapy 50-60 Gy, both in conventional 2 Gy fractions. Combinations of lateral opposing fields were used for the primary tumor site and a single anterior field with a midline block was used to treat the lower neck.

For the study group, the patients received 200 mg/m2 of Amifostine (Ethyol) diluted in normal saline by means of 50 ml. intravenous infusion over a period of 3-5 minutes daily 30 minutes before each radiation treatment. They had been hydrated orally with 500 ml. water one hour before the Amifostine administration to insure that they were not dehydrated and did not have decreased intravascular volume. Blood pressure was measured three times: immediately prior to start the infusion, immediately after the infusion, and fifteen minutes after the end of the infusion. All patients who had nausea and vomiting were evaluated for anti-emetic therapy, which consisted of administration of Metoclopramide and 5HT3 antagonist and/or fluid infusion. There was no prophylactic anti-emetic in the patients who had no experience of nausea and vomiting.

Both subjective and objective tests were used for evaluation. For the subjective evaluation, the tests were done at the baseline and on each follow up visit (weekly during treatment and at every visit after completion of the treatment for up to two years).

The first subjective evaluation was done by the patients using 100 mm visual analog scales to respond to questions concerning dryness of the mouth, the feeling of the mouth and tongue, difficulty in sleeping and the frequency of waking up to drink, difficulty in speaking without drinking water, difficulty in chewing and swallowing food, and difficulty in wearing dentures. The scores represent the patients' condition for each question during each visit. The end point was the mean score of every question of every patient during each visit.

For the second subjective evaluation, the Radiation Therapy Oncology Group (RTOG) Acute Radiation Morbidity Scoring Criteria (mucous membrane, salivary gland, pharynx and esophagus, larynx, and skin) was used to score/grade toxicity from day one through day 90. Thereafter, the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer (EORTC) Late Radiation Morbidity Scoring Criteria (mucous membrane and salivary gland) were utilized. The scoring was done by the doctor at each visit. The end point of the toxicity was the number of patients who graded $\geq$ 2 toxicity and recovered to grade 0-1 toxicity.

For objective evaluation, the authors measured the salivary gland functions by two objective tests. The first one is the measurement of the salivary flow by collecting the saliva. The specimens were collected in the following order: The patients were allowed no gustatory or mastigation stimulations for at least 60 minutes before saliva collection. Unstimulated whole saliva was defined as the amount of saliva produced for one minute without the patient's swallowing. Stimulated whole saliva was done by using 2% citrate solution applied on the dorsal tongue surface, at 30-second intervals for two minutes. The final step was the whole saliva collection for one minute. If no saliva was collected within ten minutes, the measurement was considered to be zero. The authors collected the whole saliva at the baseline of the study, at the end of treatment, and once every three months for two years. The endpoint was the mean total saliva volumes of every patient of unstimulated and stimulated saliva collection.

The most important objective evaluation to show the function of the salivary gland was the 99mTc-pertecnetate scintigraphy, which was performed before the treatment, at the end of treatment, and at six months and one year after the treatment. The 99mTc-pertecnetate scintigraphy of the salivary glands function uses a time curve to show salivary response patterns under citric acid stimulation. There were four time curve activity types. Type I, normal salivary gland function, showed the most prominent change in counts in response to acid stimulation. For type II, mild salivary gland function impairment, the change in counts by stimulation was obvious but smaller and/or more prolonged than for type I. For type III, salivary gland function impairment, only a minimal change in counts was recognized. For type IV, the non-functional salivary gland, the curve plateau showed no response to acid stimulation, representing the absence of enhanced uptake and excretion of the isotope.

The treatment toxicities at baseline evaluation and all adverse events encountered during treatment were graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0 (April 30, 1999).

The statistical evaluation data was carried out using the statistical package SPSS (Statistical Package for Social science) 9.5 for Window™ computer software (SPSS inc., 1998) and Epi Info 6. The Mann Whitney U-Wilcoxon Rank W test (Two-tailed) was used for calculating statistical differences between groups. The

Table 1. Patient characteristics and baseline evaluation and treatment

	Amifostine group n = 32	Controlgroup n = 35
Patient Characteristics		
Age (Yrs) : Mean (Min-Max)	55 (23-70)	52 (23-69)
Sex		
Male	24 (75%)	27 (77%)
Female	8 (25%)	8 (23%)
Primary Tumor site		
Oral cavity	9 (28%)	18 (51%)
Oropharynx	9 (28%)	3 (9%)
Nasopharynx	5 (16%)	8 (23%)
Larynx	5 (16%)	4 (11%)
Hypopharynx	4 (12%)	2 (6%)
Staging		
Stage I	2 (6%)	3 (8%)
Stage II	7 (22%)	10 (29%)
Stage III	16 (50%)	12 (34%)
Stage IV	7 (22%)	10 (29%)
Baseline Evaluations		
Questionnaire		
Average Score	0.61	0.5
RTOG Toxicity (Grade 0)		
Mucous Membrane	100%	100%
Salivary gland	100%	100%
Pharynx and Esophagus	100%	100%
Larynx	100%	100%
Skin	100%	100%
Whole Saliva Collection (gm / 5 min)		
Unstimulate (Average)	2.59	2.71
Stimulate (Average)	5.71	4.02
99m-Tc Pertechnitate Scintigraphy		
Type I (Normal Function)	30	27
Type II (Mild Impaired Function)	2	3
Type III (Impaired Function)	0	0
Type IV (Non-Function)	0	2*
Not done	0	3*
Treatment		
Radiation Treatment		
Definite RT	15 (47%)	18 (51%)
Post-operative RT	17 (53%)	17 (49%)
Definite RT		
Total Dose (Mean)	66.36 Gy	68.87Gy
Total Treatment Time (Mean)	53.06 Days	54.88 Days
Post-operative RT		
Total Dose (Mean)	56.43 Gy	55.59 Gy
Total Treatment Time (Mean)	43.36 Days	42.24 Days

* Five cases in the control group were excluded since they did not have baseline salivary gland function assessments or had severe pre-existing salivary gland impairment

Table 2. The subjective evaluation: Acute phase

Table 2.1. Visual analog scales (Questionnaire): Acute phase

Questionnaire : Average Score											
	Baseline	wk1	wk2	wk3	wk4	wk5	wk6	End	Mo1	Mo2	Mo3
Amifostine group	0.61	0.97	1.58	2.61	3.06	3.08	3.44	3.73	2.1	1.57	1.04
Control group	0.54	0.89	2	3.22	4.48	5.03	4.64	6.49	3.5	3.04	2.46
p-value	0.878	0.824	0.442	0.254	0.035	0.004	0.077	<0.001	0.076	0.015	0.015

Table 2.2. RTOG Acute Radiation Morbidity Scoring Criteria

Mucous Membrane (Acute Mucositis) : RTOG Grade 2-3											
%	Baseline	wk1	wk2	wk3	wk4	wk5	wk6	End	Mo1	Mo2	Mo3
Amifostine group	0	0	0	26	14	18	19	36	4	0	0
Control group	0	0	7	28	45	83	75	75	8	6	0
p-value			0.147	0.937	0.01	<0.001	<0.001	0.002	0.533	0.239	
Salivary Glands (Acute Xerostomia) : RTOG Grade 2											
%	Baseline	wk1	wk2	wk3	wk4	wk5	wk6	End	Mo1	Mo2	Mo3
Amifostine group	0	0	3	16	17	18	19	39	16	18	8
Control group	0	0	0	31	48	79	76	82	40	17	33
p-value			0.325	0.176	0.013	<0.001	<0.001	0.001	0.061	0.387	0.032
Pharynx & Esophagus : RTOG Grade 2-3											
%	Baseline	wk1	wk2	wk3	wk4	wk5	wk6	End	Mo1	Mo2	Mo3
Amifostine group	0	0	3	10	11	15	12	26	4	0	0
Control group	0	0	0	21	41	63	52	78	12	6	0
p-value			0.326	0.258	0.009	<0.001	0.003	<0.001	0.302	0.239	

Table 2.2. RTOG Acute Radiation Morbidity Scoring Criteria (Cont.)

Larynx : RTOG Grade 2-3

%	Baseline	wk1	wk2	wk3	wk4	wk5	wk6	End	Mo1	Mo2	Mo3
Amifostine group	0	0	0	0	0	0	0	4	0	0	0
Control group	0	0	0	0	12	27	16	41	8	0	0
p-value					0.096	0.008	0.083	0.002	0.213		

Skin : RTOG Grade 2-3

%	Baseline	wk1	wk2	wk3	wk4	wk5	wk6	End	Mo1	Mo2	Mo3
Amifostine group	0	0	0	0	3	4	12	3	0	0	0
Control group	0	0	0	0	3	13	28	28	0	0	0
p-value					0.98	0.248	0.163	0.477			

Chi-square Mantel-Haenszel was used for calculating statistical differences between qualitative data. A p-value of less than 0.05 was considered significant.

Results

From February 16, 1999, to September 27, 2001, sixty-seven patients with squamous cell carcinoma of head and neck cancer patients were randomized to receive radiotherapy (the control group of 35) or radiotherapy plus Amifostine (the test group of 32). There was no statistical difference in patient characteristics and baseline evaluation.

For the assessment, five cases in control group were excluded, since they did not have baseline salivary gland function assessments or pre-existing salivary gland impairment.

During the treatment period, the visual analog scales and the Acute Radiation Morbidity Scoring Criteria showed a significant difference in decrease in the severity and increase in duration of acute side effects in the Amifostine group compared to the control group.

At the end of treatment, subjective evaluation showed that the Amifostine group's analog score was lowered from 6.49 to 3.73 ($p < 0.001$), the rate of reduced grade ≥ 2 mucositis was lowered from 75% to 24% (p 0.002), the rate of reduced grade ≥ 2 acute xerostomia was lowered from 82% to 39% (p.001), the rate of reduced grade ≥ 2 pharyngitis was lowered from 78% to 26% ($p < 0.001$), and the rate of reduce grade ≥ 2 laryngitis was lowered from 41% to 4% (p 0.002). There was no significant difference in the acute skin reaction in local radiation fields. Objective evaluation showed significant impaired salivary gland function compared to the baseline, but there was no difference between the two groups.

All acute toxicities except the xerostomia had completely recovered within three months. The visual analog score was 2.46 in the control group compared to 1.04 in the Amifostine group (p 0.015). Grade ≥ 2 xerostomia persisted at 33% in the control group compared to a rate of 8% in the Amifostine group (p 0.032).

In the one-year follow-up, the grade 2 chronic xerostomia was present at a rate of 30% in the control group, but only at 5% in the Amifostine group (p 0.047). The collection of whole saliva did not show any difference. The other objective evaluation, 99mTc-pertecnetate scintigraphy of the salivary glands (the most important tool to demonstrate the salivary gland function in the present study), showed a statistical difference in favor of the study group. Parotid gland function had

returned to normal in 36.3% of the cases and was mildly impaired in 27.3% of the cases in the Amifostine group versus 9.1% and 9.1%, respectively; in the control group (p 0.034).

At the two-year follow-up, grade 2 chronic xerostomia persisted at 34% in the control group, whereas there were no cases of it in the Amifostine group.

For the Amifostine related toxicity, nausea and vomiting occurred at a rate of 64.5%, but only 25.8% needed 5HT3 antagonist therapy. Two patients had grade 3 nausea and vomiting. One of them did not respond to the anti-emetic therapy, had to stop receiving Amifostine injection, and continued with the radiation treatment alone. This same patient experienced one episode of grade 2 hypotension that was found 30 minutes after Amifostine administration. Hypotension had recovered after intravenous fluid supplementation. The authors did not find any allergic skin reactions or other complications caused by Amifostine therapy.

There was no grade 3 or 4 hematologic toxicity in both the Amifostine group and the control group.

The median follow-up time for the control group was 20.8 months (with a range of 1.9-36.9 months) and for the Amifostine group it was 25.3 months (with a range of 2.8-36.5 months). There was no statistical significance in the disease free survival rate and the disease relapse rate.

Discussion

The phase III study of the ability of the salivary gland protection against radiation treatment by Brizel D et al showed that the use of Amifostine reduced acute and chronic xerostomia when the total conventional radiation dose was 50 Gy or more. Amifostine did not reduce acute mucositis and the median duration in mucositis was similar in both groups[5].

As in that study, the authors also found a difference in acute mucosal reaction. Amifostine was of benefit during the treatment period and immediately after radiation. There is evidence that Amifostine can reduce the onset and severity of acute reaction and significantly reduce grade $\geq$ 2 mucosal reaction, including oral mucositis, pharyngitis, and laryngitis, at

Table 3. The subjective evaluation: Late phase

Table 3.1. Visual analog scales (Questionnaire): Late phase

Questionnaire : Average Score							
	Baseline	End	Mo3	Mo6	Mo12	Mo18	Mo24
Amifostine group	0.61	3.73	1.04	0.77	0.57	0.22	0.5
Control group	0.54	6.49	2.46	2	1.12	1.55	0.72
p-value	0.878	<0.001	0.015	0.007	0.439	0.011	0.757

Table 3.2. RTOG/EORTC Late Radiation Morbidity Scoring Criteria

Mucous Membrane (Acute Mucositis) : RTOG Grade 2-3							
%	Baseline	End	Mo3	Mo6	Mo12	Mo18	Mo24
Amifostine group	0	36	0	5	0	0	0
Control group	0	75	0	6	16	12	0
p-value		0.002		0.804	0.057	0.145	

Salivary Glands (Acute Xerostomia) : RTOG Grade 2							
%	Baseline	End	Mo3	Mo6	Mo12	Mo18	Mo24
Amifostine group	0	39	8	4	5	6	0
Control group	0	82	33	24	30	12	34
p-value		0.001	0.032	0.065	0.047	0.577	0.039

Table 4. The objective evaluation

Table 4.1. Whole saliva collection

Whole Saliva Collection : Average (mg / 5 min)							
	Baseline	End	Mo3	Mo6	Mo12	Mo18	Mo24
Amifostine group-Unstimulate	2.59	1.44	0.77	0.9	0.48	0.49	0.67
Control group-Unstimulate	2.73	1.1	0.64	1.57	0.16	0.1	0.43
p-value	0.589	1	0.443	0.587	0.04	0.099	0.905
Amifostine group-Stimulate	5.71	1.81	2.11	2.89	2.04	1.52	1.98
Control group-Stimulate	4.12	1.8	1.73	3.35	1.22	1.57	1.6
p-value	0.026	0.286	0.99	0.915	0.465	0.711	1

Table 4.2. 99mTc-pertecnetate scintigraphy of the salivary glands function

99mTc-pertecnetate scintigraphy								
	Baseline		End		6 Month		12 Month	
%	Amifostine	Control	Amifostine	Control	Amifostine	Control	Amifostine	Control
Type I : Normal function	100	81.8	9.1	0	27.3	9.1	36.3	9.1
Type II : Mild impair function	0	18.2	9.1	27.3	27.3	27.3	27.3	9.1
Type III : Severe impair function	0	0	54.5	45.4	36.3	54.5	27.3	63.6
Type IV : Non-function	0	0	27.3	27.3	9.1	9.1	9.1	18.2
p-value			p = 0.619		p = 0.403		p = 0.034	

the end of radiation treatment. This might be the indirect effect of there being little saliva in the mouth and throat that help in oral comfort in terms of mastigation, swallowing, and speech. It provides lubrication for the oral tissues and protects them from bacterial infections. However, in both groups the acute mucosal reaction had recovered within three months and did not correlate with late complications. This was because the basal cell layer was not completely destroyed by the total dose of 50-70 Gy. The stem cells in the basal cell layer can rapidly divide, mature, and migrate upward through the top layer and repair the mucosa in a short period after irradiation[1].

Therefore, the stem cells in the basal cell layer are quite different from the acini cells of the salivary glands, which under normal conditions do not grow or divide. For these latter, interphase cell death caused by apoptosis occurs soon after irradiation[8]. Both human and animal studies have shown that radiation injury to the salivary glands causing xerostomia and related problems primarily results from damage to serous cells, which are relatively sensitive to ionizing radiation, in contrast to mucous cells, which are more resistant[1].

The present study showed that Amifostine significantly decreased acute and chronic xerostomia. However, there was no correlation between the subjective sensation of discomfort from xerostomia and salivary flow rate or 99mTc-pertechnetate-sialography.

The 99mTc-pertechnetate scintigraphy of salivary gland function was the quantitative test to assess trapping, secretion, and excretion. In the acute phase after high dose radiation, xerostomia is predominantly manifested in failure of the excretion function, whereas in the later period, a decrease in trapping ability together with a loss in secretion function played an additional role[9]. Parotid gland function was mostly only impaired after the total radiation dose of 50-70 Gy compared to the baseline function in both study groups. At the six-

Table 5. Hematologic and non-hematologic toxicity

Table 5.1. Hematologic toxicity
Amifostine group: n = 32 210 wks
Control group: n = 35 214 wks

Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobinemia					
Amifostine group	179 (85%)	29 (14%)	2 (1%)	-	-
Control group	184 (16%)	30 (14%)	-	-	-
Leukocytopenia					
Amifostine group	180 (86%)	23 (11%)	7 (3%)	-	-
Control group	192 (90%)	15 (7%)	7 (3%)	-	-
Neutropenia					
Amifostine group	206 (98%)	3 (1.5%)	1 (0.5%)	-	-
Control group	205 (96%)	7 (3%)	2 (1%)	-	-
Thrombocytopenia					
Amifostine group	210 (100%)	-	-	-	-
Control group	214 (100%)	-	-	-	-

Table 5.2. Non-hematologic toxicity
Amifostine group: n = 32

Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hypotension	27 (74.4%)	4 (12.5%)	1 (13.1%)	-	-
Nausea	12 (37.4%)	16 (50%)	2 (6.3%)	2 (6.3%)	-
Vomiting*	14 (43.7%)	9 (28.1%)	7 (21.9%)	2 (6.3%)	-
Hot flush	15 (46.9%)	17 (53.1%)	-	-	-
Somnolence	14 (43.7%)	18 (56.3%)	-	-	-
Sneezing	19 (59.4%)	13 (40.6%)	-	-	-
Hiccup	22 (68.7%)	10 (31.3%)	-	-	-

*Antiemetics used in Amifostine group were 63% (n = 20), Metoclopramide 35% (n = 11), Ondansetron 3% (n = 1), Metoclopramide and Ondansetron 22% (n = 7) and Unknown 3% (n=1)

month follow-up, the salivary gland function showed some improvement, and favored the Amifostine group. At the one-year follow-up, more than half of the patients in the Amifostine group had normal or only mildly impaired salivary gland function due to the recovery of function in the salivary gland, especially the parotid glands, of both secretion and excretion function. A trend toward some recovery was observed after one year, while only grade 0-1 chronic xerostomia was found in the Amifostine group at the two-year follow-up.

As many have reported, salivary gland function can recover if only part of the gland was irradiated and/or the total dose was limited or a radioprotective agent was used. Liem et al showed the excretion function to be maintained in all glands irradiated at a dose of less than or equal to 25 Gy, in nearly half of the glands irradiated at a dose of 25-45 Gy, and was almost impaired at dose more than 45 Gy[10]. Kaneko et al reported that the partial recovery of salivary gland function could be expected one to two years after a total radiation dose of less than 52 Gy, even if the patients show severe xerostomia during the first six months[11]. Following these ideas, the 2 year follow-up, Wasserman, et al showed that Amifostine administration during head and neck irradiation reduced the severity and duration of xerostomia 2 years after treatment and did not compromise loco-regional control rates, progression free survival and overall survival[12]. In sum, if the acini cells can be protected and given time to recover, then the salivary gland function will recover. This refers to the remaining acini cells that were capable of repopulating within months.

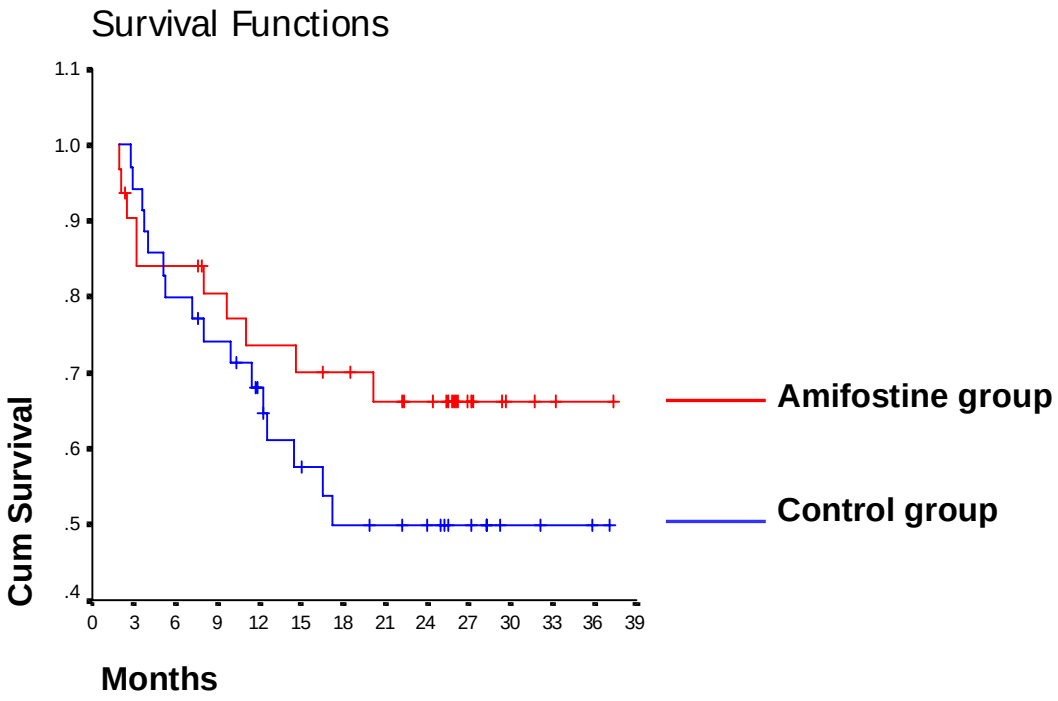

Fig. 1 Disease free survival

For the treatment toxicity, the common adverse events associated with Amifostine in clinical trials were hypotension and nausea/vomiting, but most of them were transient and mild to moderate in severity. Rades et al reported that Amifostine 200 and 340 mg/m2 used for radioprotective indication had 18% of grade 3 hypotension and 23% of grade 3 vomiting[6]. The recommendation to prevent hypotension were the careful monitoring of blood pressure, adequate pretreatment hydration, rapid Amifostine intravenous injection, and maintaining the patient in the supine or reclining position during and after Amifostine treatment. For the nausea/vomiting, individualized anti-emetic prophylaxis is concerned.

There was a review of Amifostine post marketing reported worldwide from the initial approval in 1994 to 2002. Twenty-one patients receiving Amifostine for radioprotective indication had severe cutaneous reactions. These can be classified from pruritic rash with or without fever to severe cutaneous reaction such as Stevens-Johnson syndrome and toxic epidermal necrolysis. There were too few cases to establish a dose dependent relationship. Based on all reports, from the Ethyol Cutaneous Treatment Advisory Panel (ECTAP), the estimated incidence of skin reaction was 6-9 per 10,000 patients receiving radiation therapy[7].

Among Thai patients, the most frequent complaint after injection was nausea without vomiting for three to five hours after the radiation. An anti-emetic was used for the patients who had severe nausea and vomiting. The authors recommended that they consume a large meal in the morning and have the treatment in the late afternoon. Then they could have a light meal five to six hours later. For the hypotension, the authors did not find the situation to involve complications, but the authors do recommend taking care of the patients until one hour after the injection. The authors did not find any allergic reaction or any complications caused by the drug. This was because there were not many patients in the trial. The common complications in each treatment area may be a little different, but still require careful follow-up.

In conclusion, for head and neck cancer patients who have definite radiotherapy or post operative radiotherapy, Amifostine reduced the subjective mucositis and xerostomia but did not show an objective response in the acute phase. The drug had acceptable side effects. On the long term basis, Amifostine proved effective in salivary gland preservation in both subjective and objective recovery of function. There was no anti-tumor effect. The benefit of the drug is not the same for everyone, but depends on the total radia-

tion dose, the percentage of the salivary gland involved in the treatment field, and the baseline of the salivary gland function.

The authors therefore, recommend the use of 99mTc-pertechnetate-sialography to select the patients who have baseline normal salivary gland function to get the real benefit from this radioprotective agent, Amifostine.

For the current treatment of head and neck cancer, chemoradiotherapy has been used to eliminate radiation-resistant cells to improve local control. Amifostine might reduce the interruption or delay in radiation treatment and improve the efficacy of the treatment.

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References

1. Cooper JS, Fu K, Marks J, Silverman S. Late effects of radiation therapy in the head and neck region. Int J Radiat Oncol Biol Phys 1995; 31: 1141-64.
2. Tsujii H. Quantitative dose-response analysis of salivary function following radiotherapy using sequential RI-sialography. Int J Radiat Oncol Biol Phys 1985; 11: 1603-12.
3. Franzen L, Funegard U, Ericson T, Henriksson R. Parotid gland function during and following radiotherapy of malignancies in the head and neck. A consecutive study of salivary flow and patient discomfort. Eur J Cancer 1992; 28: 457-62.
4. McDonald S, Meyerowitz C, Smudzin T, Rubin P. Preliminary results of a pilot study using WR-2721 before fractionated irradiation of the head and neck to reduce salivary gland dysfunction. Int J Radiat Oncol Biol Phys 1994; 29: 747-54.
5. Brizel DM, Wasserman TH, Henke M, Strnad V, Rudat V, Monnier A, et al. Phase III randomized trial of amifostine as a radioprotector in head and neck cancer. J Clin Oncol 2000; 18: 3339-45.
6. Rades D, Fehlauer F, Bajrovic A, Mahlmann B, Richter E, Alberti W. Serious adverse effects of amifostine during radiotherapy in head and neck cancer patients. Radiother Oncol 2004; 70: 261-4.
7. Boccia R, Anne PR, Bourhis J, Brizel D, Daly C, Holloway N III, et al. Assessment and management of cutaneous reactions with amifostine administration: findings of the ethyol (amifostine) cutaneous treatment advisory panel (ECTAP). Int J Radiat Oncol Biol Phys 2004; 60: 302-9.
8. Stephens LC, Ang KK, Schultheiss TE, King GK, Brock WA, Peters LJ. Target cell and mode of radiation injury in rhesus salivary glands. Radiother Oncol 1986; 7: 165-74.
9. Valdes Olmos RA, Keus RB, Takes RP, van Tinteren H, Baris G, Hilgers FJ, et al. Scintigraphic assessment of salivary function and excretion response in radiation-induced injury of the major salivary glands. Cancer 1994; 73: 2886-93.
10. Liem IH, Olmos RA, Balm AJ, Keus RB, van Tinteren H, Takes RP, et al. Evidence for early and persistent impairment of salivary gland excretion after irradiation of head and neck tumours. Eur J Nucl Med 1996; 23: 1485-90.
11. Kaneko M, Shirato H, Nishioka T, Ohmori K, Takinami S, Arimoto T, et al. Scintigraphic evaluation of long-term salivary function after bilateral whole parotid gland irradiation in radiotherapy for head and neck tumour. Oral Oncol 1998; 34: 140-6.
12. Wasserman TH, Brizel DM, Henke M, Monnier A, Eschwege F, Sauer R, et al. Influence of intravenous amifostine on xerostomia, tumor control, and survival after radiotherapy for head-and- neck cancer: 2-year follow-up of a prospective, randomized, phase III trial. Int J Radiat Oncol Biol Phys 2005; 63: 985-90.

ผลการให้ยา Amifostine เพื่อป้องกันการเกิดผลข้างเคียงจากการได้รับรังสีรักษา เพื่อรักษาโรคมะเร็งศีรษะและคอ

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ความเป็นมา: *ยา Amifostine เป็นยาฉีด ก่อนการฉายรังสีรักษาโรคมะเร็งศีรษะและคอ เพื่อป้องกันการทำลายต่อมน้ำลาย ช่วยลดการมีน้ำลายแห้งแบบถาวร การศึกษานี้เป็นการศึกษาในคนไทยที่เป็นโรคมะเร็งศีรษะและคอที่ได้รับรังสีรักษาเพียงอย่างเดียว หรือ ได้รับรังสีรักษาหลังการผ่าตัดแล้ว*

วัสดุและวิธีการ: *ผู้ป่วยโรคมะเร็งศีรษะและคอจำนวน 67 ราย แบ่งออกเป็น 2 กลุ่มโดยการสุ่ม กลุ่มที่ 1 ได้รับการฉายรังสีรักษาอย่างเดียว กลุ่มที่ 2 ได้รับยา Amifostine ฉีดก่อนการฉายรังสีรักษาทุกวันเพื่อลดอาการปากแห้ง วิธีการประเมินผลการรักษาทำโดย ให้ผู้ป่วยตอบแบบสอบถามเรื่องอาการปากแห้ง การให้คะแนนอาการปากแห้งโดยแพทย์ การวัดปริมาตรน้ำลาย และการตรวจการทำงานของต่อมน้ำลายโดยวิธี 99mTc-pertecnetate scintigraphy แล้วเปรียบเทียบผลการตรวจก่อนการรักษาของผู้ป่วยทั้ง 2 กลุ่ม และการตรวจในระหว่างการรักษา เมื่อสิ้นสุดการรักษา และตรวจติดตามผลเป็นระยะ ๆ อีก 2 ปี ว่ามีความแตกต่างกันอย่างไร*

ผลการศึกษา: *ผลการศึกษาพบว่าผู้ป่วยกลุ่มที่ได้รับยา Amifostine มีคะแนนเฉลี่ยการมีปากแห้ง น้อยกว่ากลุ่มที่ได้รับรังสีรักษาอย่างเดียว (3.73 และ 6.49 คะแนน) ยา Amifostine ช่วยลดการเกิด Grade $\leq$ 2 mucositis จากร้อยละ 75 เหลือ 36 และ Grade $\leq$ 2 xerostomia จากร้อยละ 82 เหลือ 39 และผลการตรวจ 99mTc-pertecnetate scintigraphy แสดงให้เห็นว่าผู้ป่วยในกลุ่มที่ได้รับยา Amifostine มีต่อมน้ำลายที่กลับมาทำงานเป็นปกติ ถึงร้อยละ 36.3 เทียบกับร้อยละ 9.1 ในกลุ่มที่ได้รับรังสีรักษาอย่างเดียว*

สรุป: *ยา Amifostine เมื่อฉีดให้ก่อนการฉายรังสีรักษาโรคมะเร็งศีรษะและคอ สามารถช่วยลดการเกิดอาการปากแห้งในระยะรักษา และช่วยป้องกันการมีอาการปากแห้งถาวรได้มากกว่าการฉายรังสีรักษาเพียงอย่างเดียว*