Original Research Paper

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Radiology

PROPHYLACTIC USE OF AMIFOSTINE TO PREVENT RADIOCHEMOTHERAPY INDUCED MUCOSITIS IN ORAL CAVITY CANCER PATIENTS

DR.K.MAHALAKSHMI PRASAD MADURAI MEDICAL COLLEGE, GOVT. RAJAJI HOSPITAL, DEPT.OF RADIOTHERAPY, MADURAI.

DR.A.KODIES MADURAI MEDICAL COLLEGE, GOVT. RAJAJI HOSPITAL, DEPT.OF RADIOTHERAPY, MADURAI.

ABSTRACT To determine the prophylactic use of Amifostine against acute mucosal toxicities in oral cavity cancer patients. Forty patients with oralcavity cancers and histopathologically proven squamous cell cancer patients were divided in two groups twenty patients each. Study group was administered with Inj. Amifostine 300mg/m2 i.v one hour before radiation and the control group only radiation. Both the group patients were given concurrent cisplatin + 5 fluoro uracil based chemotherapy. The primary end points studied were acute oral mucositis, dysphagia. The secondary end points were haematologic toxicities, treatment duration , response to treatment.

CONCLUSION: Amifostine was effective in reducing mucositis and dysphagia resulting from radiochemotherapy in patients with oral cavity cancers. Amifostine treatment did not affect the clinical outcome.

KEYWORDS :

AIM OF STUDY :

To determine the prophylactic use of amifostine against acute mucosal toxicities from radiochemotherapy in patients with oral cavity cancer patients.

PERIOD OF STUDY :

From January 2017- May 2017 – Forty patients with oral cavity cancers treated with chemoradiation were taken for study. Of the forty patients twenty patients were administered with Inj. Amifostine and twenty patients received only chemoradiation.

MATERIALS AND METHODS :

RADIOTHERAPY :

Patients were randomized to receive conventional radiotherapy 2Gy per fraction, 5 days a week, to a total dose of 60 – 66 Gy, depending on the tumor localization and TNM classification.

CHEMOTHERAPY:

Inj. Cisplatin 70 mg/m2 iv along with Inj. 5 Fluoro uracil 500 mg/ m2 iv once in 21 days cycle was given concurrently with RT.(2- 3 cycles)

RADIOPROTECTOR:

Inj, Amifostine 300 mg/m2 iv was administered in the study group(Twenty patients) 1 hour before going for radiation. The primary end point was the grading of acute mucosal toxicities, dysphagia, and secondary end points included treatment duration, hematologic toxicity and clinical outcome.(1,2)

SELECTION CRITERIA :

1. The patients were limited to locally advanced stage III – IV oral cavity cancers.
2. Histopathological proved squamous cell carcinoma.
3. Performance status 1-2
4. No comorbidities
5. Not willing for surgery.

SUBSITE CLASSIFICATION OF PATIENTS :

1. Carcinoma Tongue – 3
2. Carcinoma buccal mucosa - 6
3. Carcinoma floor of mouth – 3
4. Carcinoma lower alveolus – 3
5. Carcinoma hard palate – 2
6. Carcinoma upper gingivum - 3

RESULTS OBSERVED :

1. Mucositis, dysphagia – as per RTOG grading – during treatment.
2. Treatment duration
3. Hematologic toxicity
4. Clinical assessment of Complete response or partial response .

a. After completion of concurrent chemoradiation.(Radical RT + 2-3 cycles chemotherapy)

RESULTS:

MUCOSITIS:

RTOG Scoring Criteria:

Grade	Description
0 (none)	No change over baseline
I (mild)	Irritation, may experience slight pain, not requiring analgesic
II (moderate)	Patchy mucositis that may produce inflammatory serosanguinitis discharge; may experience moderate pain requiring analgesia
III (severe)	Confluent, fibrinous mucositis, may include severe pain requiring narcotic
IV (life-threatening)	Ulceration, hemorrhage, or necrosis

Mucositis was observed both in control group and amifostine given group. But the intensivity of mucositis was little high in the control group. Patients who received Inj Amifostine experienced only gr I – II mucositis and there was only minimal interruption of treatment. But patients in control group experienced gr III mucositis and had more interruption of treatment.

3 – 4 TH WEEK (TD 30 – 40 GY)

Grading of mucositis	Amifostine group (20pts)	Control group (20 pts)	P value
Grade I	NIL	5 (25%)	0.0093
Grade II	NIL	6 (30%)	0.002
Grade III	NIL	NIL	NIL
Grade IV	NIL	NIL	NIL

4 – 5 th week (TD 40 – 50 GY)

Grading of Mucositis	Amifostine group(20 pts)	Control Group(20 pts)	P value
Grade I	2 (10%)	6 (30%)	0.025
Grade II	NIL	7 (35%)	0.002
Grade III	NIL	7 (35%)	0.002
Grade IV	NIL	NIL	NIL

Acute toxicities (mucositis and dysphagia) were less severe in the amifostine treated group. After 15 fractions of radiation most of the patients in control group experienced grade 2 mucositis compared with none of the patient in the amifostine treated group. By week 5 i.e at 25 fractions , in the control group nearly 90 % of the patients experienced grade 2 – grade 3 mucosal toxicities, whereas in the amifostine administered group only 10 % experienced mucosal toxicities.

TREATMENT DURATION:

Treatment Duration	Amifostine group(20 pts)	Control group(20 pts)
6 weeks	16	NIL
7 weeks	4	12
8 weeks and more	NIL	8

The treatment duration was significantly shorter in the amifostine treated group because interruptions were more frequent in the control group due to mucositis. Oral mucositis was treated with supportive care medicines like antibiotics, anti-inflammatory and sodium bicarbonate solutions.

HAEMATOLOGIC TOXICITY :

The following were the haematologic toxicities experienced by both the groups during treatment.(3,4)

1. Anaemia
2. Neutropenia – Grade I, Grade II only.
3. Thrombocytopenia – very rare <2 %

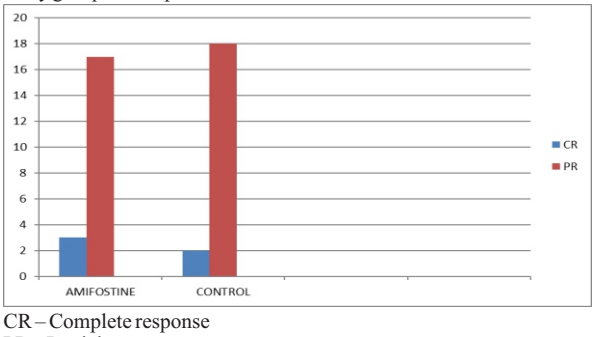
TOXICITY		AMIFOSTINE GROUP(20 pts)	CONTROL GROUP (20 pts)	P VALUE
ANEMIA		7	7	-----
NEUTROPENIA	GRADE I	9	10	0.37
	GRADE II	3	2	0.05
THROMBOCYTOPENIA		1	1	-----

There was no relationship observed between hematologic toxicity and Inj Amifostine. All the patients in the study received chemotherapy and experienced some form of hematologic toxicities during their treatment. All patients were treated with supportive care like transfusions, colony stimulating factors as required .

RESPONSE TO TREATMENT:

	AMIFOSTINE GROUP(20 pts)	CONTROLGROUP
COMPLETE RESPONSE	3	2
PARTIAL RESPONSE	17	18

Of the forty patients treated with concurrent chemoradiation more than 80 % of patients had only partial response this may be due to the extensive involvement of the disease and its response to treatment. No correlation was found significant between Amifostine administered study group and response to treatment.



CR – Complete response
PR – Partial response

DISCUSSION :

Radiotherapy plays a significant role in the management of head and neck squamous cell carcinoma patients, either as definitive radiotherapy or adjuvant radiotherapy. The mucositis, acute or late xerostomia caused by radiation are the most common toxic effects which usually interrupts the planned course of treatment. Mucositis is an acute non haematologic toxicity that occurs during the treatment; xerostomia usually develops acutely during chemoradiotherapy. And persists for a long time.

For the past several decades, researchers have been investigating use of drugs to decrease the side effects during radiotherapy, so as to increase the amount of radiation that can be safely administered to the patients. The most clinical used radioprotective drug is amifostine that was initially developed as a part of the nuclear warfare program. Based on some randomized controlled trials , it is shown that amifostine could reduce acute and chronic xerostomia in HNSCC patients treated with radiation or concomitant chemoradiotherapy. (5,6,7,8)

The most common nonhematologic side effects of radiochemotherapy in head and neck cancer patients are mucositis and xerostomia. These side effects cause great discomfort to the patient and many treatment approaches have been investigated, including povidone-iodine mouth washes, mucosa- adhesive antimicrobial polymer films and others. In addition , radioprotective drugs may be used to reduce the toxicities associated with radiochemotherapy. A recent review by an expert panel of the American Society of Clinical oncologists recommended that amifostine use be considered to decrease the incidence of acute and late xerostomia in patients who undergo fractionated RT in head and neckregion. However, additional studies are needed to evaluate fully the efficacy of amifostine against radiochemotherapy induced toxicities. (3,4)

In our study, we administered amifostine on all RT days. This regimen reduced the severity of radiochemotherapy induced toxicities compared with the control group and has increased the patients tolerance of radiochemotherapy. Additionally, with this regimen, 90.9% of patients in the study group achieved a partial response , with significantly reduced mucositis, dysphagia, and xerostomia levels compared with those in the control group. This suggests that radiochemotherapy with amifostine administration before RT was well tolerated and highly effective.Although the volume of parotid glands included in the radiation fields was not measured, the patients entered in our study had an extensive primary tumor of the oral cavity which obliged us to include >75% of the parotid gland in the treatment fields.

In our study the incidence of mucositis was less pronounced in the amifostine treated group than in patients in control group with only 10 %of the former showing sign of mucositis by week 6 of follow up compared with only >90% of the 20patients in the control group. Additionally amifostine delayed the onset of acute mucositis and reduced its rate of progression. Mucositis generally develops at the end of second week of treatment with RT and remains until therapy completion. The study group developed mucositis at a slower rate than did the control group with most patients remaining at least one toxicity grade lower than those in the control group through out the length of the study. A similar but less pronounced, effect was observed with dysphagia, including a lower rate of symptom progression in the amisostine group that showed greater significance as the treatment neared completion. Weight loss was not evaluated in our study, but dysphagia was one of our end points and it leads to weight loss.(7,8)

These results suggest that amifostine may be effective in reducing the level of acute toxicities induced by radiochemotherapy. The incidence of xerostomia was significantly reduced by amifostine . The magnitude of this effect suggest that the most potent prophylactic effect of amifostine against radiochemotherapy induced side effects is the protection against onset of acute oral mucositis and also against Xerostomia. Although the volume of the parotid glands included in the radiation fields was not measured, the patients entered in our study had an extensive primary tumor of the oral cavity, which obliged us to include >75% of the parotid gland in the treatment field. This effect is important, because current treatments are only palliative in nature. The decreased salivary output resulting from RT in the area of salivary glands may lead to changes in oral flora and a higher risk of dental caries. Because radiation induced xerostomia can linger or may become irreversible, it is desirable to minimize its occurrence with a prophylactic therapy. In our study the effects of Xerostomia was assessed only by taking history and was just considered as an observation and due to logistics salivary flow test couldn't be done and hence it was not taken as secondary end points.(1,2,5,6)

In our study the haematological toxicities observed were anaemia, neutropenia and thrombocytopenia. There was no correlation with amifostine administered group and control group. Both the group experienced equal morbidity as faras haematologic toxicities are considered.(3)

In our study , amifostine administration significantly reduced the duration of radiochemotherapy treatment compared with the control group. At week 5-6 a significantly greater number of control patients, compared with the study patients, had interrupted treatment because of mucositis. It has been suggested that interrupting or delaying RT(5,7) has an adverse effect on treatment efficacy and will negatively affect the clinical outcome. Further more interruptions to RT regime may allow tumor cell repopulation and affect local tumor control.

CONCLUSION:

Amifostine was effective in reducing mucositis and dysphagia

resulting from radiochemotherapy in patients with oralcavity cancers. Amifostine treatment did not affect the clinical outcome.

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