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CONCURRENT CISPLATIN 5FU BASED CHEMOTHERAPY AND RADIOTHERAPY IN ADVANCED MUCOSAL SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

Radiotherapy

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ABSTRACT

One hundred and thirty four patients with locally advanced head and neck squamous cell carcinoma were prospectively studied from June 2012 – May 2013 at Department of radiotherapy , Govt Rajaji Hospital and Madurai Medical College. All patients received concurrent Cisplatin + 5FU based chemotherapy(CT) along with standard radiotherapy(RT).The initial complete response (CR) was 71 % and partial response was achieved in rest 29% of the cases. The 4 yrs locoregional control was 45% for those patients who achieved complete response . Acute treatment related toxicities included one death due to renal damage . The late toxicities noticed were xerostomia in 40% of patients. The results justify that concomitant use of cisplatin + 5FU based chemotherapy along with radiotherapy is a effective and accepted standard of care in locally advanced head and neck cancer patients in tertiary care centre.

KEYWORDS

INTRODUCTION:

Carcinoma of the head and neck, represented mainly by the mucosal squamous cell carcinoma in the upper respiratory and digestive tracts, accounts for approximately 40,000 cases a year in India. Results of treatment of these tumors are inversely proportional to the extent of the disease. The probability of maintaining tumor free status in the head and neck by 5 yrs ranges from 80-90% for T1N0 lesions in larynx, to approximately 15 % in T4N3 tumors that are located in the base of tongue or the hypopharynx.

Among the factors that the RTOG has found important in achieving initial CR and maintaining tumor free status with time are the following: Karnofsky performance status(KPS), stage of the disease, primary site and initial response to radiotherapy.

The RTOG has conducted a number of prospective studies with the objective of improving tumor control and survival in these tumors, among which RTOG 81-17 is included. The RTOG 81-17 study determined the feasibility of a concurrent combination of moderately high dose systemic cisplatin + 5 FUchemotherapy and radiotherapy in advanced squamous cell carcinoma of the upper respiratory and digestive tracts. Previous group experience had revealed that sequential systemic methotrexate chemotherapy and radiotherapy was not better than radiotherapy alone. A national intergroup study conducted with the participation of the RTOG compared surgery and postoperative radiotherapy versus chemotherapy with cisplatin and bleomycin, followed by surgery and postoperative radiotherapy and resulted in no overall improvement with the use of chemotherapy. (1,2)

MATERIALS AND METHODS:

Patients with mucosal squamous cell carcinoma of the oralcavity, oropharynx, hypopharynx, nasopharynx, laryngopharynx and maxillary sinus, American joint Committee stages III and IV, Karnofsky performance status > 50, adequate renal function, and no plan for the resection of the primary tumor after irradiation. In essence, we included laboratory studies that would show adequate hematologic status and adequate renal and hepatic functions and imaging studies that would exclude distant metastasis and could help in the staging of the primary tumor. Bilateral audiograms, triple endoscopy to rule out other concomitant lesions and dental care were required.

Chemotherapy consisted of three courses of cisplatin administered every three weeks, beginning on day 1 with radiotherapy. Cisplatin 70 mg/m2 was given in 500ml of 5% dextrose as infusion along with 5 fluorouracil 750mg/m2 intravenous bolus infusion along with supportive medicines like potassium chloride, magnesium sulphate and hydration with normal saline for a period of three hours. Measurements of fluid intake and output were maintained for 48 hours after cisplatin administration, and longer periods of hydration of additional fluids were given to match any excessive emesis or urinary output when necessary. Antiemetics such as prochlorperazine were administered either as suppository or intramuscularly 30 minutes before cisplatin and every 4 hours thereafter as necessary. Dose modifications or discontinuation of cisplatin were predicted on hematologic, neurologic system , or renal toxicity. Dose adjustments for hematologic and renal toxicity were based on leukocyte count values. Cisplatin was discontinued unless complete recovery from renal toxicity occurred. Hematologic toxicity required return of leukocyte count to 4000 and platelets to 100,000 before treatment was continued. In the event of moderate myopathy, moderate weakness, peripheral neuropathy or seizure, the dose of cisplatin was reduced by 40 %.(3)

Radiation was started on day 1 at 180-200cGy per day, 5 days a week until total doses ranging from 6000 – 6600 cGy were delivered. Radiation portals were designed to include the entire primary and bilateral lymphnodes chains with the upper borders set at least at the posterior aspect of the mastoid process. Boost to persistent primary tumor could be given after 5400 cGy using photons. A minimal dose of 5000 cGy was delivered to clinically negative lymph nodes. Minimal doses of 6000-6600 cGy were delivered by external beam, to nodes less than 2 cm, 2 – 4 cm, > 4 cm respectively. Treatment interruptions were allowed only for healing of severe normal tissue reactions such as confluent mucositis. Surgery was permissible only in those instances where lymphnodes originally exceeded 3 cm. The salvage surgery for persistent tumor was performed atleast 6 weeks after completion of radiotherapy. Complete blood counts,Blood urea, Serum creatinine were performed weekly and before each subsequent course of chemotherapy, then monthly for 3 months after therapy. Performance status, weight and symptoms were recorded at specific times by the protocol. Instances of toxicity due to both radiotherapy and or chemotherapy were carefully recorded and graded.

The endpoints of the study included the initial tumor response (CR), acute toxicity due to radiotherapy and or chemotherapy, total disease control rates and absolute survival rates. The RTOG toxicity grading system was used. Patients were considered to have achieved initial CR induced by irradiation and chemotherapy when both the primary and the nodal disease disappeared after radiotherapy and chemotherapy without intervening surgery for residual disease. Evaluation of tumor status was made by physical examination, supplemented by repeat endoscopies and radiographic studies when pertinent and biopsies. If there was intervening surgery after radiotherapy and chemotherapy, the patient was considered a CR by salvage surgery.(4,5,6)

The patients who did not achieve an initial CR were considered to have treatment failures on study day 1. Patients who did achieve a CR were

considered to have failed treatment on the first day when locoregional recurrence and or new metastatic disease was reported. Even though subsequent therapy may have cleared the disease, the treatment was considered to be failure. With respect to survival analysis , the treatment was considered to have failed if the patient died regardless of the cause of death. Complications were graded from 0(none) to 5 (fatal). Toxicities of grade 3,4, and 5 were considered major. Differences in initial response rates were evaluated by the chi square test.

RESULTS:

Patient registration on this study occurred from June 2012 – May 2013, Of the 134 patients, 124 were available for analysis. The reasons for exclusion were as follows: Ineligibility due to lower stage, second primary, compromised renal function, incomplete data for evaluation, cancelled because of retrospective entry, refusal of treatment.

The median follow up was 34 months. Only five patients have survived beyond 5 years at the time of this analysis, consequently no 5 year survival rates can be calculated.

The characteristics of the patients were as follows;

Stage III	18 %	22 Pts
Stage IV	82%	102 pts
Age	Mean 58 yrs	Median 58 (25-79)
KPS	100 – 5% 90-59% 80 – 21% 70 – 10% 60 – 4% 50 – 1%	6 pts 74 pts 26 pts 12 pts 5 pts 1 pt
Primary site	Oropharynx Nasopharynx Oral cavity Hypopharynx Larynx Paranasal sinuses	49 pts 28 pts 23 pts 8 pts 8 pts 8 pts
Differentiation of Histologic type	Undifferentiated Well differentiated Moderately differentiated Poorly differentiated	15 pts 21 pts 51 pts 37 pts

INITIAL TUMOR RESPONSE:

A complete disappearance of tumor from the head and neck (CR) was observed in 71%, (88 of 124), of patients; and CR after salvage surgery was observed in 2 % of patients. The overall CR with salvage surgery was 73%.The patients with KPS below 70 had inferior CR rates (33%) . Nasopharynx showed the best CR rate (89%) as compared with the hypopharynx (37%). Poorly differentiated lesions had 94% CR versus 64% in the well differentiated and moderately differentiated. The patients with a primary of the oral cavity or the hypopharynx showed a significantly poorer CR rate 50 %(15/30) versus 80 % (75/94), p= 0.0032. Patients with no keratinization identified on the review of the histopathologic slides showed a CR of 93%(41 patients) versus 63%(73 patients) when some keratin was identified in the microscopic picture , P=0.001.

CHARACTERISTIC	TOTAL EVALUABLE	CR NO.	PERCENTAGE
Sex Male	96	68	76
Female	28	22	79
KPS 90-100	80	61	76
70-80	38	27	71
<70	6	2	33
Stage III	23	18	78
IV	100	72	72
T stage T1	7	7	100
T2	12	9	75
T3	47	34	72
T4	58	40	69
N stage N0	28	27	79
N1	21	16	76
N2	26	18	69
N3	48	34	71
Primary site	51	37	73
Oropharynx	27	24	89
Nasopharynx	22	12	55
Oral cavity	8	3	37
Hypopharynx	8	7	87
Larynx	8	7	87
Paranasal sinuses			

The CR rates by T and N stages are included in table. All T1 patients had disappearance of tumor even though accompanied by N2 or N3 nodes.Advancing T stage with N2-3 status showed decreasing CR rates. The T1-2 patients had a CR of 93 %(14/15) versus 64 %(18/28) for T3 and 64%(20/31) for T4 patients. In patients No status, the CR was 90%(9/10) for T3 and 72 % (13/18) in T4. The extent of nodal involvement did not affect the CR in T3-T4 patients with positive nodes. In patients with N0 stage the CR rate was 79%(22/28) versus 76% with N1(16/21), 69% with N2(18/26), and 71 % with N3(34/48). In N3 patients the T status did not influence the CR; in T4N3 lesions 76% showed CR (16/21) versus 58% with T3N3 (11/19) and 88 % (seven of eight) with T1-2.

	Number	Percent
Radiotherapy delivery Completed RT(>6450cGy)	107	86
Chemotherapy Delivery Received three courses Received two courses Received one course	75 29 20	61 23 16
Combined modality delivery RT(>6450+CT 3 courses)	72	58
Not completed Patient refused Prohibitive toxicities Patient deteriorating Condition Disease Progression Other	52 14 22 7 4 5	42 11 18 6 3 4

TOXICITY:

The acute toxicities have been reported. The common toxicities reported were stomatitis, dry mouth, leucopenia, thrombocytopenia. Xerostomia accounted for 40% of toxicities.

Eighty six percent of the patients received a minimum dose of 6450 cGY or higher . Chemotherapy toxicity did not interfere with radiotherapy delivery. In 20 % (21/107) of patientscompleting radiotherapy according to group standard, the elapsed time took longer than 70 days. In 15 patients the reason cited was either toxicity or refusal .Delivery of three courses of chemotherapy was achieved in 58% of patients. In 18% of patients, treatment was not completed because of toxicity limitations.

Tumor Control and survival rates(%)

Control/survival	1 year	2 year	3 year	4 year
Tumor control	56	46	43	43
Locoregional control	53	41	38	37
Total				
Absolute Survival	68	52	43	34

DISCUSSION:

The Yield of radiation therapy alone in advanced mucosal squamous cell carcinoma of the head and neck decreases with increasing stage of the disease. For some advanced lesions, combinations of surgery and radiation are feasible, but a significant percentage of these tumors are not surgically resectable and the alternative of using initial radical radiotherapy reserving surgery for salvage seems to show almost equal long term results as combined radiation and surgery used preoperatively or postoperatively. The use of combination of cisplatin with 100mg/m2, every 3 weeks for three doses during radiotherapy, has been quiet tolerable. As shown in the above table the 4 year survival rates have been superior with the use of concurrent chemoradiation.

CONCLUSION:

The results justify that concomitant use of cisplatin + 5FU based chemotherapy along with radiotherapy is a effective and accepted standard of care in locally advanced head and neck cancer patients in tertiary care centre.

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