

Neo-adjuvant chemotherapy with cisplatin and short infusional 5-FU in advanced head and neck malignancies

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ABSTRACT

Background: Combination of radical surgery and radiotherapy is the standard management of head and neck malignancies. But due to considerable morbidity of surgery and associated cosmetic and functional deficiencies, often aggravated by adjuvant radiotherapy, many patients prefer only radiotherapy with its' decreased chance of survival. Proper surgical facilities are also not accessible to most of our patients. Neo-adjuvant chemotherapy and loco-regional management by surgery and / or radiotherapy have emerged as a viable alternative.

Aims: The purpose of this study is to find out the survival outcome as well as toxicity profile of Neo-adjuvant chemotherapy with cisplatin and short infusional (3 hours) 5-FU followed by radiotherapy in advanced head and neck malignancies.

Materials and Methods: From June 2002 to December 2003, seventy four patients with advanced head and neck malignancies were planned to be treated with Cisplatin (50 mg / sq. meter) on Days 1 and 2 and 5 – FU (600 mg / sq. meter) on Days 1, 2 and 3 by 3 hour infusion on Day care basis. On completion of four cycles of chemotherapy at 21 days interval, all patients were destined to receive 6000 cGy of radiotherapy to the loco – regional site.

Results: At one year follow up on completion of therapy, 57% patients were alive and 31% patients were disease free. These 31% patients enjoyed a good quality of life in terms of cosmetic and functional deficits. Toxicities were moderate and easily manageable.

Conclusion: The study indicated that neo-adjuvant chemotherapy with Cisplatin and short infusional 5 – FU may be delivered on day care basis and results are comparable with Cisplatin and 96 hours continuous infusional 5 – FU. Thus avoiding the continuous infusional 5 – FU, 7 to 10 days in-patient hospitalization during each cycle may be avoided which is a constrain in developing countries like us.

Key words: Advanced H and N Malignancy, Neo-adjuvant chemotherapy, Cisplatin and short infusional 5-FU

INTRODUCTION

Carcinoma of the head and neck region is the 5th most common malignancy world wide^[1] and is probably more common in Indian sub - continent due to increased use of smoking and chewing tobaccos. Stage of the disease at the time of diagnosis appears to be the most important prognostic factor in its' management. For small primary tumors (T 1,2) without regional lymph node metastasis (N 0), curative surgery or radical radiotherapy are both equally effective. For more extensive primary tumors (T 3,4) or for those with regional metastasis (N +) radical surgery and adjuvant radiotherapy improves survival at the price of major functional deficit. Loss of natural speech is the chief forfeit of surgery along with inability to smell or sneeze (in case of tracheal stoma), a diminished sense of taste and problems of swallowing. Upfront radiation preserves the voice and cosmesis at the price of decreased chance of survival. Though planned combination of pre- or post operative radiation and complete

surgical excision remained the management of choice in advanced head and neck cancers,^[2] proper surgical facilities are not accessible to majority of our patients. Some opt to receive the less effective therapy of radiation alone to avoid radical surgery. They risk shorter survival rather than face increased survival with severe surgical morbidity and functional and cosmetic deficits.

Although optimal surgery and / or radical radiotherapy have improved both local and regional control, they have not been translated into improved survival. Two years after standard treatment, clinical evaluations indicated that less than 40% of the patients remain disease free. Local recurrence and / or regional lymph node metastasis are diagnosed in 60% and distal metastasis are found in 15-25% patients. The rate of distal metastasis is actually far greater.^[3] These compelling problems are responsible for the emerging importance of primary chemotherapy.

Since the introduction of cisplatin in 1970s,

chemotherapy regimens combining cisplatin with a variety of other drugs used before surgery and / or radiotherapy have shown improved overall response rates in head and neck malignancies. Bleomycin and 5 - FU appeared to be the two most common agents used along with cisplatin. In most studies, 5 - FU has been used as a 96 or 120 hour continuous infusion that required 7-10 days in-patient hospitalization during each cycle. In an effort to deliver cisplatin and short infusional (3 hours) 5 - FU on day care basis to avoid in-patient hospitalization and thereby to reduce infrastructure requirement and to evaluate the efficacy and toxicities of short infusional 5 - FU and cisplatin as neo-adjuvant chemotherapy to radiation, we started a short prospective non randomized trial with 74 patients of advanced head and neck cancers and this is the preliminary report of our experience at a follow up of one year.

MATERIALS AND METHODS

From June 2002 to December 2003, seventy four patients with head and neck malignancy were included in a prospective non randomized trial of neo-adjuvant chemotherapy followed by radical radiotherapy in the department of radiotherapy of Nilratan Sircar Medical College and Hospital. Inclusion criteria were:

1. Histologically proved squamous cell carcinoma of head and neck and cytologically proved lymph node metastasis, when lymph node is clinically palpable.
2. Age : 30 to 60 years.
3. Karnofsky performance status : ≥ 70 .
4. Stage – III or IV disease.
5. No lung metastasis as shown in chest X-ray.
6. Normal haematological, renal and hepatic functions as follows:
 - (a) Haemoglobin ≥ 11 gm%,
 - (b) Total leukocyte count ≥ 4500 / cu.mm.
 - (c) Platelet count $\geq 1,50,000$ / cu.mm.
 - (d) Total bilirubin ≤ 1.5 mg%
 - (e) Serum creatinine ≤ 1.5 mg%
7. Patient could not have any surgery, radiotherapy or chemotherapy for the current disease nor have any previous malignancy.
8. Informed consent.

Patient characteristics have been shown in Table 1.

Site and extent of the primary disease was assessed clinically, by indirect / direct laryngoscopy and by CT scan, whenever possible. Lymph node status was assessed clinically. Staging was done as per UICC criteria. Concomitant upper GI tract malignancy was excluded by endoscopy. Extent of the disease of the 74 patients has been shown in Table 2.

Treatment schedule: On entering the study and extent of the disease assessed carefully, patients entered into the induction chemotherapy protocol. All patients received

Table 1: Clinical profile

Age (years)	
Median :	47
Range :	32 to 59
Sex	
Male :	62
Female :	12
Karnofsky performance status	
90 :	33
80 :	22
70 :	19
Primary site	
Oral cavity :	10
Oropharynx :	22
Supra glottic larynx :	26
Hypo pharynx :	16

Table 2: Distribution according to the stage (n = 74)

'T' stage	N 0	N 1	N 2	N 3
T 1	Nil	Nil	Nil	Nil
T 2	Nil	02	04	Nil
T 3	06	18	22	08
T 4	08	04	02	00

- 1) Injection 5 - FU 600 mg / sq. meter of body surface area in one bottle of normal saline infused over a period of 3 hours daily for 3 consecutive days (Day-1 to Day-3).
- 2) Injection Cisplatin 50 mg / sq. meter of body surface area in two bottles of normal saline infused rapidly on Day-1 and Day-2.
- 3) Injection Granisetron 3 mg I.V very slowly given daily for the three days (Day-1 to Day-3) before starting chemotherapy, and oral Granisetron 1mg twice daily on Days 4 and 5.
- 4) Injection Mannitol (20%) 100 ml infused rapidly on Day-1 and Day-2 for diuresis.

Patient was encouraged to take oral fluid as much as possible on days of chemotherapy and thereafter.

Same chemotherapy schedule was repeated every 21 days for four cycles. Complete blood count and serum creatinine estimations were done 2 / 3 days before each chemotherapy cycle and patients must have a Hemoglobin ≥ 9 gm%, TLC ≥ 3000 / cu. mm, Platelet count $\geq 1,00,000$ / cu. mm and creatinine ≤ 1.5 mg% before the next course could be administered. Courses were delayed week by week until these values are reached.

Extent of the disease (both primary and regional lymph node) was measured before each chemotherapy cycle by both the radiation oncologist and E.N.T specialist. After completion of four cycles of chemotherapy, patients were given a rest period of three weeks for hematological recovery and then radical radiotherapy was delivered by parallel opposing lateral beams with appropriate wedges to the original disease site (by shrinking field technique) to a total dose of 6000cGy over a total period of 40 days, by Cobalt – 60 machine, daily single dose being 200cGy, 5 days per week regimen.

Patients who had discontinued chemotherapy even after a single cycle, either due to toxicity or due to their unwillingness to continue further, were also treated with External radiotherapy as above.

Evaluation and follow up: Throughout the course of radiation therapy, patients were monitored weekly by the radiation oncologist for tumor response and for normal tissue reactions. Complete blood count was done weekly during the radiation therapy and periodically in the follow up period as clinically indicated until hematological recovery was documented. Adverse reactions were documented as per ECOG toxicity criteria.

After completion of the therapy, patients were examined at 6 weeks interval for the first 6 months and then at 12 weeks interval for the rest period. Routine history and physical examination by the radiation oncologist, indirect / direct laryngoscopy by the ENT specialist, Chest X-ray and fiber optic examination when ever possible, were part of the routine follow up.

Responses: After completion of therapy, patients who had no clinical evidence of disease either at the primary site or in the regional lymph nodes nor had any evidence of distal metastasis, were considered as 'complete remission' (CR). Those who had $\geq 50\%$ decrease of the tumor size and regional lymph node were considered as 'partial remission' (PR). $\leq 25\%$ change of the tumor size in either direction were considered as 'no response' (NR) and $> 25\%$ increase of the tumor size or appearance of new tumor were considered as 'progressive disease' (PD).

RESULTS

Although 74 patients were enrolled into the study, only 62 patients completed the proposed 4 cycles of chemotherapy. Rest discontinued chemotherapy after a varying number of cycles mostly due to their unwillingness to continue further.

Though all the patients who entered the study were advised to undergo radiation therapy, only 64 patients participated in the external radiation therapy protocol, of which 58 patients had completed the proposed 4 cycles of chemotherapy. Of these 64 patients, 56 completed the proposed radiation course and 08 patients discontinued mostly due to mucocitis. The toxicity profile as per ECOG scale has been shown in Table 3.

Though severe hematological toxicities were noted in some patients, no death occurred during or after treatment that can be attributed to the toxicities. To combat hematological toxicities, all patients with Grade-III toxicity were given packed cell transfusion or granulocyte colony stimulating factor (G-CSF) support or platelet transfusion as indicated. Acute mucositis or epidermitis were troublesome in some patients particularly near the completion of the radiation, but they disappeared within three weeks of completion of treatment with supportive care.

Response and Survival: Response rate was evaluated in all 64 patients at 6 weeks after completion or discontinuation of radiation therapy. 34% (22) patients achieved C.R, 44% (28) achieved P.R and 22% (14) were in no response or progressive group. At one year follow up only 42 (57%) patients were available for evaluation and rest were considered dead, though that may not be true as the level of disease consciousness of our patients as well as our follow up infrastructure are far from adequate. However at one year follow up 31% (20/64) patients were disease free, 33% (21/64) had loco regional disease and 2% (01/64) had distal metastasis in addition to loco regional disease.

DISCUSSION

Optimization of loco regional control in patients with head and neck carcinoma remain a challenging problem to the radiation oncologist as well as to the surgical oncologist. Despite surgical resection and post operative radiotherapy with its' consequent morbidity and functional deficits, or primary radiotherapy to the maximally tolerated doses, loco regional recurrences remain the major pattern of treatment failure.^[4,5] Again primary radiation therapy to maximally tolerated doses has always been delivered by hyper fractionated regimen in which radiation is to be given at least twice daily at 6 hours apart, which is almost impossible in our set up due to infrastructure deficiencies. Whether improvement in loco regional control will ultimately be transmitted to increased survival or not, is a matter of considerable debate.^[6,7]

Theoretically one of the major causes of failure of radiation to control large tumors, whether primary or secondary is the presence of hypoxic malignant cells at or near the center of the tumor and their decreased radio sensitivity.^[8] Neo-adjuvant chemotherapy down stage the tumor, improves intra tumor blood circulation and thereby reduces the percentage of malignant hypoxic cells making them more ra-

Table 3: Heading acute haematological, cutaneous and muscosal toxicities (n = 64)

Grade of Toxicity	Mucositis		Acute skin reactions		Anaemia		Leucopenia		Thrombocytopenia	
	No	%	No	%	No	%	No	%	No	%
I	10	16	24	38	18	28	22	34	32	50
II	38	59	34	53	42	66	35	55	30	47
III	16	25	06	09	04	06	07	11	02	03
IV	00	00	00	00	00	00	00	00	00	00

dio-sensitive. At the same time impact of neo-adjuvant chemotherapy on the low but finite incidence of distal metastasis is also a theoretical advantage.

It was recognized that like other solid tumors, previously untreated patients with head and neck malignancies respond to chemotherapy almost twice as often as patients who has previously undergone surgery and/or radiotherapy.^[9] This increased responsiveness is probably due to better performance status found in previously untreated patients and to the presence of intact blood supply undisturbed by previous surgery and/or radiotherapy.^[10]

In 1997, Harari^[11] reported the results of a mail survey of 300 community cancer specialists which attempted to identify the most frequent treatment for patients with loco regionally advanced non-metastatic squamous cell carcinoma of head and neck. The single most common treatment approach proved to be induction chemotherapy with 5 - FU and cisplatin followed by radiation. Physicians cited a desire to improve both loco regional tumor control and overall survival using this treatment schedule.

Mercier et al^[12] treated 53 patients with advanced (Stage III and IV) squamous cell carcinoma of head and neck with cisplatin and 5 - FU. They used cisplatin 100 mg / sq. meter intravenously on Day-1 followed by a 96 hours continuous infusion of 5 - FU 1000 mg / sq. meter / day. Cycles were repeated every 21 to 28 days for 2-3 courses and then patients were offered surgical resection, if feasible and/or radiotherapy. In a subgroup analysis they found 15% CR and 12% PR in previously untreated patients after chemotherapy. But among their patients who completed the loco regional therapy also, a 54% CR was achieved. However this high CR rate was not translated into increased overall survival and median survival of all patients was only 11 months.

In a randomized study Rooney et al^[13] compared efficacy of 96 versus 120 hours continuous infusion of 5 FU along with cisplatin in advanced previously untreated squamous cell carcinoma of head and neck. After 3 cycles of induction chemotherapy, all patients received local therapy in the form of surgery and/or radiotherapy. In their study 120 hours continuous infusion of 5 - FU definitely showed a survival advantage over 96 hours infusion. At 18 months, 62% were alive in 120 hours group versus 40% in 96 hours group.

Decker's et al^[14] found a 94% response rate (CR - 63%, PR - 31%) after 3 cycles of cisplatin and 120 hours continuous infusional 5 - FU. Their patients were subjected to local therapy in the form of surgery and/or radiotherapy after 3 cycles of chemotherapy. In spite of the high response rates, a survival benefit was not documented in their series, though the follow up period was very short (Range 2 to 10 months).

In our study, at one year 57 % of the patients were alive and if we consider only those patients who underwent radiotherapy even after a single cycle of chemotherapy, then

31% of those patients were disease free. Since these patients have not undergone any surgical intervention, they enjoyed a good quality of life without any functional or cosmetic deficit. A fact also emerged from this study that none of the patients with N3 lymph node achieved CR or was alive at one year.

The present study was not free from certain drawbacks e.g.

1. It was not randomized.
2. The study group was heterogeneous in respect to primary tumors.
3. Patients' number was small to achieve a statistically significant result.
4. Drop out at each level of study was high.
5. Surgical resection facilities were not available to non-responders to chemotherapy.

However, this study indicated that four cycles of cisplatin and 3 hours 5 - FU infusion may be given on day care basis and thus avoiding the inpatient infrastructure requirement that is very essential to developing countries like us. The toxicities are low and easily manageable, and at the same time may achieve a result comparable to cisplatin and 96 hours continuous 5 - FU infusion. A large randomized study is needed to judge the efficacy of our chemotherapy dose schedule and at the same time whether combining it with higher radiation doses by hyper fractionated schedule will produce better result or not.

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Job opportunities

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