LEAD ARTICLE

Abstract

50 patients of advanced squamous cell carcinoma of the head and neck were randomised either to receive chemotherapy followed by radiation therapy or chemoimmunotherapy followed by radiotherapy. In the chemoimmunotherapy arm, the patients received recombinant interferon alpha 2b 3 M.U. subcutaneously, thrice a week on alternate days for 5 weeks from Day 1, Cisplatin 70 mg/m² on Day 1 and 21, and 5-fluorouracil 1000 mg/m² on Day 1, 2, 3 and Day 21, 22, 23, followed by from Day 36, radiotherapy by Cobalt 60 to a tumour dose of 65 Gy in 30 # over 6 weeks. In the control arm, patients received Cisplatin 70 mg/m² on Day 1 and Day 21, 5-fluorouracil 1000 mg/m² on Day 1, 2, 3 and Day 21, 22, 23 followed by radiotherapy by Cobalt 60 to a tumour dose of 65 Gy in 30 # over 6 weeks from Day 36. Only Grade II and III toxicity was observed in the two arms which were manageable. Patients treated with chemoimmunotherapy followed by radiotherapy showed 60% complete response, 20% partial response and 12% no change/progressive disease; while the patients on the control arm treated with chemotherapy and radiotherapy showed 12% complete response 44% Partial response and 32% no change/progressive disease. This trial concludes that chemoimmunotherapy followed by radiotherapy is an excellent alternative therapeutic strategy for the management of advanced head and neck cancers with manageable toxicity.

Keywords

(Chemoimmunoradiotherapy, Chemoradiotherapy, Head and Neck Cancer)

Comparative Evaluation of Chemoimmunoradiotherapy and Chemoradiotherapy in the Management of Advanced Head and Neck Cancer

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It has been estimated that by the turn of the century in the year 2001 A. D. there will be 806,000 new cancer patients in India, out of which 70,000 would be cancers of the head and neck ⁽¹⁾. The radiotherapy department of Safdarjung Hospital sees about 2500 new cancer cases every year, about 35% being cancers of the head and neck. In a country with low levels of education, lack of awareness and poor health consciousness, unfortunately most of these patients present with advanced disease. While head and neck cancers are responsive to conventional modes of treatment namely surgery, radiotherapy and chemotherapy either singly or in combination, the outlook for advanced disease remains rather gloomy as the conventional modes of treatment appear to be inadequate for the management of advanced stage disease ⁽²⁾. Defects in the immune system have been implicated in the aetiopathogenesis of head and neck cancers ⁽³⁾. While much more requires to be understood about the immunological response to cancer before the full potential of the immunotherapy could be employed in the therapy of head and neck cancers, however, some of the existing evidence, does, suggest that the immune system plays a role, and that biological response modifiers do have a role in the treatment of advanced head and neck cancers. ² A pilot study undertaken in the interferon research unit has shown excellent results with a combination of Interferon, cisplatin and 5-fluorouracil followed by radiotherapy ⁵. Hence it was decided to undertake this present study to define the role of chemoimmunotherapy followed by radiotherapy in the management of advanced head and neck cancers.

Materials and Methods

50 Histologically proven locally advanced (Stage III & IV) cancer of head and neck which included cancers of the pharynx, larynx, mouth and oral cavity, nose and PNS, were recruited into the trial from June 1, 1994. The eligibility criteria for recruitment into the trial was as follows:

- (a) histologically proven squamous cell carcinomas of head and neck,
- (b) locally advanced (stage III & IV) with measurable disease,
- (c) surgical resection not possible,
- (d) age between 25–70 years,
- (e) karnofsky's performance status of at least 70%
- (f) haemoglobin of at least 10 gm,
- (g) TLC of at least 4000/mm and platelet count of at least 100,000 / mm,
- (h) adequate renal function
- (i) no hepatic enzyme derangement,
- (j) no associated medical condition which could affect treatment like diabetes mellitus, pulmonary tuberculos is etc.
- (k) no concomitant second malignancy,
- (l) no previous oncological treatment except biopsy.
- (m) informed consent

Pre-treatment patient work up included a detailed history, complete general physical examination, ENT examination, which includes indirect laryngoscopy, nasopharyngoscopy, or endoscopic evaluation as indicated, complete blood counts, blood urea and serum creatinine, liver function tests, serum electrolytes, X-ray chest, plain radiographs of relevant regions and C. T. Scan as indicated to define the extent of disease. Patients were randomised to either receive the study protocol of chemoimmunotherapy followed by radiotherapy or the control protocol of chemotherapy followed by radiotherapy. The treatment protocols of the two arms of the trial are as follows :

(a) Study Protocol

- (1) Recombinant interferon alpha 2b 3 M.U. subcutaneously thrice a week (on alternate days) for 5 weeks from Day 1.
- (2) Cisplatinum 70 mg/m² after adequate hydration on Day 1 and Day 21.

- (3) 5-flurouracil 1000 mg/m² in a 4 hour infusion on Day 1,2,3 and Day 21, 22, 23
- (4) Tab. paracetamol 500 mg half hour prior to interferon administration.
- (5) Locoregional radiotherapy from Day 36 by Cobalt 60, at 80 cm. SSD , to a tumour dose of 65 Gy in 30 # over 6 weeks.

(b) Control Protocol

- (1) Cisplatinum 70 mg/ m² after adequate hydration on Day 1 an Day 21.
- (2) 5-flurouracil 1000 mg/ m² in a 4 hour infusion on Day 1,2,3, and Day 21, 22, 23
- (3) Locoregional radiotherapy from Day 36 by Cobalt 60, at 80 cm. SSD, to a tumour dose of 65 Gy in 30 # over 6 weeks.

Adequate antiemetic therapy was given to all patients receiving chemotherapy with cisplatinum and 5-flurouracil. Assessment of response and toxicity were made as per the WHO criteria⁶.

Observations and results

50 patients were entered into the trial, 25 receiving the study protocol and 25 receiving the control protocol. There were 38 male and 12 female patients, with a mean age of 52.6 years (range 26–70 yrs.) and with a mean performance status of 82.3% (range 70–100%). The site of lesion in the two arms is shown in Table 1.

Table-I Site of lesion		
	Study group	control Group
Larynx	10 (40%)	7 (28%)
Base of Tongue	5 (20%)	5 (20%)
Maxilla	3 (20%)	5 (20%)
Tonsil	3 (12%)	3 (12%)
Cheek	2 (8%)	3 (12%)
Nasopharynx	2 (8%)	2 (8%)

Toxicities in both arms of the trial were manageable and shown in Table 2. No Grade IV

toxicity was reported and patients could be managed with conservative treatment. No patient required

Table-II
Toxicity
Only Grade II & III

	Study group	control Group
Neutropaenia	16 (64%)	12 (48%)
Thrombocytopaenia	13 (52%)	10 (40%)
Mucositis	15 (60%)	12 (48%)
G.I. Disturbances	18 (72%)	15 (60%)
Dehydration	5 (20%)	3 (12%)
Electrolyte Imbalance	4 (16%)	3 (12%)

interruption of treatment or postponement of planned treatment protocol and no dose reduction was carried out. However, 2 patients in the study protocol died, 1 due to severe electrolyte imbalance during chemoimmunotherapy and 1 due to severe cardiomyopathy during fourth week of radiotherapy. In the control protocol 2 patients died during chemotherapy due to progressive disease and 1 patient died due to myocardial infraction during second week of radiotherapy.

We observed 15 (60%) complete response, 5 (20%) partial response and 3 (12%) no change/progressive disease with the study protocol compared to 3 (12%) complete response, 11 (44%) partial response and 8 (32%) no change/progressive disease with the control protocol. Failures according to site in the study protocol and control protocol are shown in Table III.

Table-III
Site of lesion

	Study group	control Group
Larynx	1	2
Base of Tongue	1	3
Tonsil	1	1
Cheek	--	1
Nasopharynx	--	1

Discussion

The study protocol was designed with the fact that interferons biomodulate the chemotherapeutic agents cisplatinium and 5-flurouracil^(7, 8, 9). We felt addition

of interferons to cisplatinium and 5-flurouracil would result in enhanced effects which would result in better downstaging of disease thereby making it amenable to locoregional treatment, radiotherapy being the locoregional treatment we selected. Cisplatinium and 5-flurouracil in combination has been found to be one of the most effective chemotherapy protocol in the management of head and neck cancers.¹⁰ However though the use of induction chemotherapy has shown good results, these have not been translated into overall survival benefits.

We felt if we are able to sufficiently downstage locoregionally advanced head and neck cancers to make them treatable by radical radiotherapy, we may be in a position to achieve survival benefits. Since patient accrual into the trial commenced from only June 1, 1994, we are not in a position to comment on survival benefits which chemoimmunotherapy may give to the patients. The results of the study protocol are very encouraging and superior to the results of the control protocol with a response rate of 80% compared to 52% in the control. The percentage of complete response with the study protocol of 60% is statistically significant when compared to other combination therapy protocols reported in literature in the management of advanced head and neck cancers. Toxicity in both arms of the trial were manageable as no Grade IV toxicity was seen in any patient. However, we were concerned with the two deaths during the treatment with the study protocol. One death occurred due to electrolyte losses in the form of sodium, potassium and calcium, which could be the result of increased renal tubular effects of Cisplatinium in the presence of interferons. The death occurred due to severe cardiomyopathy which could also be indicative of enhanced cardiac effects of cisplatinium and 5-flurouracil due to interferons. This leads us to feel that in future trials we may be required to downscale probably the dose of cisplatinium and 5-flurouracil during chemoimmunotherapy. The results of this trial also brings forward the role of immunomodulation of interferons. The excellent results observed in the chemoimmunotherapy group in the present trial, and in view of the fact that defects of the immune system have been implicated in the aetpathogenesis of head and neck cancers, suggest that immune mechanisms do have a role to play in the management of head and neck cancers². As we have

not looked at immune mechanisms and the immune response in patients of head and neck cancer receiving interferons, we can not comment on this aspect. Also there does not seem to be literature available documenting immune aspects of patients of head and neck cancer receiving interferons. We plan to attempt immunophenotyping and study the immune response in our future trials, so that we may be able to comment on immune aspects. While we continue to accrue further patients into the trial and look at the follow-up, we feel larger studies in a cooperative multicentric setting could benefit by enrolling a large

number of patients into the trial. Long term follow-up is being studied carefully before we are in a position to definitely comment on overall survival. In future, with large numbers and better follow-up together with data on immunophenotyping we may be able to make some definitive observations. However, this study definitely indicates that chemoimmunotherapy followed by radiation therapy does appear to be an attractive alternative therapeutic strategy for the management of advanced head and neck cancer with manageable toxicity.

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