Induction followed with concurrent chemo radiotherapy in advanced head & neck cancer

ABSTRACT

Background: The need for effective, well tolerated, and convenient therapies for inoperable Head and Neck cancer has led researchers to continually refine chemotherapeutic regimens with radiotherapy to balance efficacy with safety and tolerability in order to maintain or improve quality of life and chemotherapy either induction or concurrent with radiation have emerged as viable alternative.

Aim: This study was performed to analyze the efficacy and safety of induction chemotherapy with radiotherapy and concurrent radiotherapy on survival, functional and quality of life outcomes.

Material and Method: From Dec. 2001 to July 2003, hundred inoperable Head & Neck cancer patients were planned to be treated with methotrexate, Bleocon and cis-platin. On completion of 3 cycles at 21 days interval, after 2 weeks of last cycles, fifty patients were planned to receive only radiotherapy (Group A) and rest 50 patients (Group B) were given cisplatin 50 mg weekly before Rt. on every Monday. All 100 patients received radiotherapy (66-70 cGy) to the locoregional sites by cobalt 60 units.

Result: After completion of therapy in group A complete response was observed in 56% patients which was 68% in group B. After 2 years of follow up only 54% patient alive and 34% patients were disease free in group A whereas in group B. 60% patient alive in which 42% were disease free. The survived patient enjoyed good quality of life.

Conclusion: Patients responded better with induction chemotherapy can be treated with radiotherapy and those who failed to show satisfactory response may be treated with concurrent chemo radiotherapy to get additional benefit in term of survival with good organ preservation along with acceptable and manageable occurrence of schedule & dose related adverse events.

KEY WORDS: Inoperable Head and Neck cancer, induction chemotherapy, concurrent chemo radiotherapy, prolong infusions

INTRODUCTION

The worldwide incidence of head and neck cancers exceeds half a million cases and ranked 5th most common malignancies[1]. Its annual number of new cases in United States is approximately 40,000 accounting for 5% of the adult malignancy. In Indian sub continent due to use of smoking and chewing tobacco the incidence in more than 25% of all malignancies. More than 80% of the head and neck malignancy present in locally advanced stages and carry a poor prognosis and this has remained unchanged over the past 30 years. Surgery followed with post operative radiotherapy is the standard treatment of such patients with 30% cure rates. The main reason for the failure is local recurrence in about 80% of patients and 20% distant metastasis and patients survive at the price of major function defect. Over-all survival of untreated advanced stage head and neck cancer patients ranged from 1 day to 53.8 months (median 3.82 months). In any treatment option which should be accepted worldwide, survival should be 4+6 months longer than expected for untreated cases and improve the quality of life with manageable toxicities.[2]

Majority of patients suffering with advanced stage of Head and Neck cancers are inoperable as they risk shorter survival rather than face increased survival with severe surgical morbidity and function and cosmetic deficit. Unavailability of surgical facilities and expenditure over surgery are the another factor. Less than 40% of such treated patients remain disease free. Because the critical location of most of the neoplasm of Head and Neck interferes with breathing, eating and speaking at last stage of illness, the cosmetic &
functional implication of therapy often weigh heavily in treatment decision. The high risk of loco regional failure (≥60% cases) and probability of distant metastasis (≥20% cases) are responsible for the emerging importance of primary chemotherapy.

Chemotherapy for advanced head and neck cancer has rapidly progressed since the early 1960 and methotrexate has remained a standard treatment for this cancer for almost 20 years both as single agent or in combination with other drugs with varied response rate from 24 to 75% with 29% cumulative response. With Bleomycin response rate is very conflicting and varied from 6 to 93% with a cumulative response rate of only 18%. Cisplatin in one of the most extensive agent effective in the management of SCC head and neck which can be used either single agent or combined with variety of other drugs and have shown improved overall response range from 23 to 71% with a cumulative rate of 28%. Methotrexate, Bleomycin and 5FU are the most common drugs used with Cisplatin in most studies before radiotherapy. To enhance the over all response rate with acceptable toxicities, recent randomized trial using cisplatin as a single agent given concurrently with RT have shown some encouraging result.

Based on increased radio responsiveness to chemotherapy seen in untreated patients and probability of tumor shrinkage which improve local control, induction or neo adjuvant CT schedule was designed and with the anticipation that the induction component will reduce the rate of distant metastasis where as the concomitant schedule will enhance the probability of loco regional control, this perspective non randomized trial with 100 patients of advanced head and neck cancer was initiated and this is the preliminary report of our experience at a follow up of 2 years.

MATERIALS AND METHODS

During a period from Dec. 2001 to July 2003, 100 patients of head and neck cancer attending the department of Radiotherapy, Gandhi Medical College, Bhopal were included in a prospective non randomized trials of induction chemotherapy followed by either radial radiotherapy alone (Group A) or with concurrent chemo radiotherapy (group B).

Eligibility Criteria were
1. Histopathologically confirmed SCC head and neck.
2. Performance status >60%.
3. Age <70 years.
4. Not exposed to surgery, chemotherapy and radiotherapy for the current disease.
5. Stage III or IV.
7. Normal haemotocrit.
8. Normal renal and liver function.
9. Informed consent.

Patients characteristic are shown in Table 1. Site and size of the primary disease was assessed after a course of antibiotics and anti inflammatory drugs, was given. It was done clinically by inspection direct / indirect laryngoscopy and by other appropriate studies if required e.g. CT Scan etc. Clinically lymphnode status was assessed and TNM staging was done as per UICC criteria. Complete blood profile haemoglobin and platelet count, Blood urea, serum creatinine were done before each course of chemotherapy.

Treatment Designed
Treatment schedule is designed to optimize clinical efficacy and minimize the occurrence of schedule and dose related adverse events in patients and after proper evaluation, all the 100 patients received induction chemotherapy and following drugs were given.
1. Inj. Methotrexate 50 mg IV Bolus day 1
2. Inj. Bleomycin 15 mg IV Bolus day 1
3. Inj. Cisplatinum 120 mg IV 6 hours infusion day 1
4. Other supportive drugs.

All patients were encouraged to take plenty of oral fluids after chemotherapy. Same chemotherapy schedule was repeated at an interval of every three weeks and such 3 cycles were administered. Complete blood count, serum creatinine and blood urea were done before each course of chemotherapy and when it was within normal limits only than chemotherapy drugs were administrated. Cisplatin was given in 6 hours infusion.

Table 1: Patient characteristics

<table>
<thead>
<tr>
<th>Age</th>
<th>Group A No.</th>
<th>Group B No.</th>
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<td>31-40</td>
<td>5</td>
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<td>41-50</td>
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<td>51-60</td>
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<td>61-70</td>
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<td>45</td>
<td>84</td>
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<th>Group B No.</th>
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<td>43</td>
<td>85</td>
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<tr>
<td>Muslim</td>
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<td>07</td>
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<th>Group B No.</th>
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<td>66</td>
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<tr>
<td>Tobacco+Other</td>
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<td>20</td>
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<tr>
<td>No addiction</td>
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<th>Group B No.</th>
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<tr>
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<tr>
<td>Oropharynx</td>
<td>07</td>
<td>10</td>
<td>17</td>
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<tr>
<td>Laryngopharynx</td>
<td>18</td>
<td>20</td>
<td>38</td>
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<tr>
<td>Maxillary antrum</td>
<td>01</td>
<td>03</td>
<td>04</td>
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<td>Stage</td>
<td>Group A No.</td>
<td>Group B No.</td>
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<td>IV</td>
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Yogi V, et al.: Induction followed with concurrent chemo radiotherapy
After completion of 3 cycles of induction chemotherapy status of disease was assessed and patients were given 2 weeks rest for recovery and then in 50 patients (group A) radical radiotherapy was delivered to the original disease sites by parallel opposing lateral beams by shrinking field technique and total dose of 60 to 70 Gy in 33 to 35 fraction over 7 weeks was given with supportive management for mucositis. Fields were planned to cover primary site as well as whole neck and after 46 Gy fields were reduced to exclude spinal cord. In rest 50 patients (Group B) radiotherapy was given as in group A but concurrently 50 mg cisplatin was infused weekly for 6 wks. in 4 hours infusion before radiotherapy on every Monday.

Evaluation of Follow Up
Before each course of induction chemotherapy patients were evaluated and during radiotherapy they were seen weekly by Radiation oncologist for normal tissue reaction and tumor response. Routine investigations were performed and if required supportive management was given. As per RTOG criteria adverse reaction was documented. During chemotherapy all patient were admitted in ward.

After radiotherapy completion patients were examined and then they were examined first after 6 wks followed by 3 months interval for 2 years by Radiation oncologist or if required, by other specialist also. Blood count x-ray chest fiber optic examination were also done if needed. Patients belong to rural area were also motivated to come for regular follow up.

Response
If there was complete disappearance of all visible and palpable tumor without evidence of distant metastasis after completion of induction chemotherapy and or radiotherapy they were considered as complete response (CR) and where there was >50% regression of the two longest perpendicular diversion of the lesion or nodes, they were grouped under partial response (PR) Rest were considered as stable disease (SD) or progressive disease (PD) if there was progression of tumor or nodes size or appearance of any distal metastasis. Response in summarized after induction chemotherapy in table 2 and after complete treatment including radiotherapy response is summarized in table 3.

RESULT
All the 100 patients were evaluated before each course for normal tissue reaction and after 2 weeks completion of 3rd cycle of induction chemotherapy response was analyzed which is shown in table 3

Out of 100 patients, 50 were advised to receive ext. Radiotherapy only (Group A) and with manageable toxicities they completed the course of Radiotherapy. Rest 50 patients were given weekly cisplatinum 50 mg before ext. radiotherapy for 6 cycles on every Monday. Objective response was evaluated after completion of radiotherapy and the same criteria for response was followed which in shown in Table 4.

Subjective response was also assessed in the form of sense of well being and relief from symptom which could be complete, patient or no change. Mild to severe mucositis and hematological toxicities was noticed in all the patients but it was manageable. There was no death during course of therapy due to adverse reaction. All the patient who developed mucositis or hematological toxicities were kept in ward till the recovery even after radiotherapy and in some patients of group B receiving chemo radiotherapy were admitted upto two weeks after complication of radiotherapy.

Response and Survival
Objective response after induction chemotherapy was evaluated in all 100 patients and then equally divided into two groups as sown in table 2.

6 weeks after completion of radiotherapy in group A, CR, PR and RR/PD was observed in 56%, 28% and 16% respectively which were 68%, 22% and 10% respectively in group B. Surprisingly the patients who did not responded with induction chemotherapy, were also radio-resistant in group A. It was also observed that the patients who responded partially with induction chemotherapy were responded better with concurrent chemo radiotherapy because in group B out of 30 patients who responded partially, 19 patients showed CR after RT (Table 4).

At two year follow up only 27 (54%) patients in group A and 30 patients (60%) patients in group B were reported and they were considered alive out of which 17 (34%) patients were disease free in group A whereas in group B 20 patient (40%) were disease free. Advantage of concurrent chemo radiation in more observed in poorly responded patients

| Table 2: Response after induction chemotherapy in both groups |
|-----------------|---------|--------|        |
| Response        | Group A | Group B | Total  |
| CR              | 12      | 13     | 25     | 25%    |
| PR              | 30      | 30     | 60     | 60%    |
| NR/PD           | 8       | 7      | 15     | 15%    |

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<th>Table 3: Response after radiotherapy</th>
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<td>Response</td>
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<tr>
<td>CR</td>
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<td>NR/PD</td>
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<th>Table 4: Follow up after 2 years</th>
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<td>Response</td>
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<td>Follow-up</td>
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with induction chemotherapy. Patients responded better with induction chemotherapy were good responded in both the group. So for normal tissue reaction is concern it was more marked in Group B (Table 5) but it was accepted for the response benefit, which help in improving quality of life with organ preservation in both the groups.

DISCUSSION

In developing country like India more than 60% patients of head and neck SCC presenting with advanced disease and carry a poor prognosis which has remained unchanged over the past 30 years. When presenting disease is either inoperable or patients refuse surgical management role of radiotherapy is limited and remain a challenging problem to the Radiation Oncologist. With primary radiotherapy, even with maximum tolerated dose, locoregional recurrence remain the major pattern of treatment failure.[6,7] Wheather improvement in loco regional control will ultimately be transmitted to increase survival or not, is a matter of considerable debate.[8,9]

In primary tumour or in lymph nodes, the presence of hypoxic malignant cells at or near the center of the tumor may be responsible for radiation failure as there was decreased radio sensitization.[10] Induction chemotherapy improve the blood circulation in tumor by decreasing tumor burden (Chemo down staging) and hence growth fraction in tumor also increases making them more radio sensitive by killing more dividing cells. Simultaneously induction chemo also kills micrometastasic cells if present undetected in body at the time of initiation of treatment. Theoretically during radiotherapy chemotherapeutic drugs (cisplatinum) may extravasate through the radiation induced altered tumor vasculature, hence promote better drug delivery to the tumor site and in anoxic cells population which is major cause of treatment failure. After seeing the unusual sensitivity to chemotherapy in recurrent or metastatic tumor, it was also tried in advanced but untreated patient with H & N Cancer and it was observed that untreated patients respond twice as patients treated prior with Surgery or Radiotherapy.[11] This may be because of presence of intact blood supply.[12]

Since 1992 six Metaanalysis trial have been performed and result of four (Stell 92, Munro 95, Sayed 96 and MACH & NC 98)[13-16] revealed small but significant benefit from the use of chemoradiotherapy in head and neck cancer (MACH & NC) collaboratively group reviewed 63 randomized trial and noticed survival benefit of 4% in 6 years median follow up with concurrent regimen.[17] One randomized trial of concurrent chemoradiotherapy over 88 patients of H & N Ca. (50 mg cisplatinum weekly with RT) revealed that median survival and 5 yr survival were both superior in chemo radiotherapy group (22 m Vs 40 m) and (13% Vs 36%) but the rate of distant metastasis was similar with lower rate of Loco regional failure with combined therapy (41% vs 23%).[18] Vokes et al. (2003)[19] formulated 3 major goals with the induction chemotherapy plus concurrent chemoradiation (1) increased survival rates (2) organ preservation (3) reduction of systemic metastasis as a site of treatment failure.

Ervin et al.[20] conducted study were 29 patients with two courses of an intensive chemotherapy regimen consisting of MTX, BLM and Cisplatinum with low toxic effect which was manageable. CR was noted in 7 patients (27%) response was rapid occurring within 3 weeks from the initiation of chemotherapy and it was maximum at 6 weeks. Weichselbaum et al.[21] employed induction chemotherapy with cisplatin BLM and MTX followed by Surgery and / or Radiotherapy. They noticed 19% CR and 81% partial response in first 23 patients. Mucocitis was also noticed in 48% patients.

Zidan et al.[22] treated 31 patients of advanced head and neck cancer with 3 courses of combination chemotherapy using BLM, MTX and Cisplatin followed by a radical course of radiation. Of 29 evaluable patients, four (14%) achieved CR, 13 (45%) had a PR. With the addition of radiotherapy and surgery the CR rate increased to 27%.

Shridhar et al.[23] treated 59 patients with advance head and neck cancer with induction chemotherapy consisting of high dose MTX, Leucovorin, BLM and Cisplatinum and pointed out that response to chemotherapy prior to Surgery and or Radiotherapy was excellent in patients with T4 tumour, provided basis for further intensive treatment.

Clavel et al.[24] performed randomized trial in 185 patients with four drugs (Cisplatin, BLM, MTX and VCR) and compared with 3 drugs (BLM, MTX and VCR). They observed CR in 16% with four drug which was only 5% in 3 drugs which was without cisplatinum. They supported indirectly the superiority of cisplatinum combination.

Olasz L et al.[25] performed the randomized trial in 38 patients with four drugs regimen consisting of cisplatin BLM, MTX and VCR and compared with 3 drugs which include BLM, MTX and VCR and observed clinical regression in 87% cases with 24% CR. They also pointed that those received four drug showed more microscopic regression.

Ensilver et al.[26] pointed out that patients with 50% reduction in tumour volume after cisplatinum combination.
therapy were responded better to subsequent radiotherapy which means chemosensitive tumour may also be radiosensitive.

Karp and Colleagues [27] reported in overall response rate of 27% to induction chemotherapy followed with radiotherapy in advance stage head and neck cancer patients. After 2 years local control was achieved in 52% with organ preservation advantage. With the concept that induction Chemotherapy reduces loco regional burden of tumour and facilitate the ultimate complete eradication by radiotherapy, microscopic systemic disease eradication, and prediction about outcome of cure and organ preservation, many trials were performed with an overall response rate often exceeding 75% and it become the standard organ preserving treatment in head and neck cancer (Vokes 2003, Rischino 2003) [28-29]. Though concomitant CT RT seems to be more successful approach than induction CT followed with RT, some promising advantage has been observed with the addition of induction chemo therapy to a concurrent chemoradiotherapy treatment regimes (Vokes 92, Clerk 97 and Kies 98) [30,31,32]. Non-availability of various drugs their high cost, poor socioeconomic status of patients left us to find out the outcome with available, acceptable drugs with proven efficacy like MTX, BLM and cisplatin as an induction followed with cisplatin as concurrent. This combination has been proved effective in the management of SCC head and neck because survived patients offered a good quality of life without any functional or cosmetic deficit, however some drawback was also present in this study.

1. It was not randomized.
2. Number of patient in less
3. Study period in short
4. Follow up is poor.
5. Cause of death of patient is not known.

This study indicate that 3 courses of MTX, Bleomycin and 6 hour infusion of cisplatin can be given as induction chemotherapy with manageable adverse effect in the management of SCC of head and neck for better outcome and further non responder can be managed with concurrent CT-RT so that radio resistant foci of tumor can be benefited with concomitant chemotherapy and chemo-resistant cells can be killed by radiotherapy. However a large randomized study is needed to pin point if any, superiority of induction chemotherapy plus concurrent chemo-radiotherapy over induction chemotherapy plus radiotherapy or only chemoradiotherapy in term of survival, locoregional failure, incidence of distant metastasis and quality of life.

Chemotherapy and radiotherapy controlled only tumour and tumour related death. It cannot improve the expected age, hence cause of death in every treated cancer patients should be evaluated.

REFERENCES

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Announcement—Forthcoming Event

International Clinical Hyperthermia Society
XXVIII ICHS Annual – Convention

Date: 6th & 7th January 2007
Venue: Mumbai

The meeting will address and audit the role of Hyperthermia in Oncology
Topics to be covered are:

1. Clinical Trials Of Hyperthermia & Radiation
2. Chemo Radiation & Hyperthermia
3. Hyperthermia with Chemotherapy
4. Evolving Technology of Hyperthermia
5. Nanotechnology of Hyperthermia

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Confirmed Speakers:
1. Dr. Takeo Ohinishi - Japan
2. Dr. Cobi Van Der Zee – The Netherlands
3. Dr. H Kampina – The Netherlands
4. Dr. Alvaro Martinez - USA
5. Dr. Haim Bicher - USA
6. Dr. Giammaria Fiorentini – Italy
7. Prof. Milton Yatvin – USA
8. Dr. Preetam Kumar - USA