

Research Article

Retrospective study on efficacy and safety of nanoparticle paclitaxel and concurrent radiotherapy in patients with advanced head and neck cancer

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ABSTRACT

Background: Advanced (Stage III and IV) Squamous Cell Carcinomas of the head and neck (SCCHN) produce severe functional impairment, considerable morbidity, and significant mortality. Over the past 2 decades, organ-sparing efforts using either induction chemotherapy or concurrent chemotherapy and radiotherapy (RT) have become popular and have demonstrated equivalent or superior survival rates compared with surgery and/or RT alone, with a survival rate of approximately 40% at 5 years. Although the addition of chemotherapy to RT enhances toxicity, randomized trials and meta analyses have documented improved survival clearly compared with the results from RT alone. Initially, most combinations included once-daily RT combined with cisplatin either alone or with 5-fluorouracil (5-FU). There was number of toxicities of high grades associated with these drugs, and also difficulty in their administration. We have retrospectively studied nanoparticle paclitaxel with RT on concurrent setting as an alternative.

Methods: We have retrospectively studied data of patients of advanced SCCHN treated with nanoparticle paclitaxel along with RT. Nanoparticle paclitaxel was administered at a dose of 80 mg/m² over one hour infusion once weekly along with RT, 60 Gray (Gy) in 30 fractions, five days per week, over 6 weeks.

Results: Total numbers of patient in this study were 28 with median age of 49 years. 78.57% of patient had stage IV disease and 21.43% stage III. Overall response rate was 68% with complete response (CR) in 29% and partial response (PR) in 39%.

Conclusions: The use of nanoparticle paclitaxel along with RT is safe, feasible, efficacious and cost effective. Intensive randomized studies with large sample size are required in this direction.

Keywords: Advanced SCCHN, Concurrent chemo-radiotherapy, Nanoparticle, Paclitaxel

INTRODUCTION

Squamous cell carcinoma is the most frequent tumor of head and neck region. Head and neck cancers are the sixth most common cancer worldwide.¹ About two third of these in developing country with highest rate in South Asian countries such as India and Shrilanka. 80% patients presents with advanced loco-regional disease (stage III &

IV).² 5 year relative survival rate is 81% for localized early disease and 59% for all stages combined.³

For early stage head and neck cancer radiation therapy or surgery are treatments of choice depending upon site of tumor. For advanced stages combined modality with surgery and/or radiotherapy (RT) plus combination of chemotherapy in neoadjuvant, concurrent or adjuvant

setting is used. Although the addition of chemotherapy to RT enhances toxicity, randomized trials and meta-analyses have documented improved survival clearly compared with the results from RT alone. For these reasons, the design of this study was focused on, how best to combine chemotherapy with RT for the treatment of patients with advanced squamous cell carcinoma of the head and neck. (SCCHN).

Cisplatin, 5-fluorouracil, Carboplatin, Docetaxel, Paclitaxel, Vinorelbine, Gemcitabine, Cetuximab and Nimotuzumab had been used in various combinations with RT either in weekly or three weekly regimens, with variable efficacy and toxicity profiles. These drugs have more infusion related and other adverse reactions, require so many drugs for premedication, more intravenous fluids, making it difficult for administration on day care basis. Especially in department with heavy patient load.

Conventional paclitaxel infusion is formulated in a vehicle of 50% ethanol and 50% polyethoxylated castor oil, commercially known as "Cremophor EL," to overcome the problem of poor water solubility.^{4,5} However, this vehicle has been implicated in a number of adverse drug reactions (ADRs) associated with paclitaxel, including acute hypersensitivity manifesting as respiratory distress, hypotension, angioedema, urticaria, and rash.^{6,7}

Nanoparticle paclitaxel has no infusion related reactions and no other adverse effects compared with normal paclitaxel. It has comparable clinical outcome and is economical too.⁸ So in this study nanoparticle paclitaxel was used along with RT and its safety and efficacy were evaluated.

METHODS

Total numbers of patient in this study were 28 (treated between July 2010 to August 2011). We have analyzed data to assess the efficacy and safety of nanoparticle paclitaxel concurrent with radiation versus radiation therapy alone in patients with advanced squamous cell carcinoma of head and neck. Selection of patient was done by following criteria:

Inclusion Criteria:

- Age between 18-75 years, both males and females.
- Patients without any prior chemotherapy, radiotherapy and surgery for the tumor.
- Histopathologically or cytologically confirmed advanced (stage III/IV) SCCHN.
- Patients having tumors of the oral cavity, oropharynx, hypopharynx, larynx, and nasopharynx.
- Life expectancy \geq 12 weeks.
- ECOG Performance Status (PS): 0-2.
- Measurable stage III / IV disease (at least one target lesion of \geq 2cm).
- Patients who can provide written informed consent.

- Patients with adequate bone marrow, renal & hepatic function.

Exclusion Criteria:

- Pregnant women and lactating/ nursing mothers.
- Brain and/or distant metastases and other concomitant malignancies.
- Participation in other study within 30 days of study entry.
- Major systemic disease which might confound the study.

Criteria for Withdrawal:

- Patient requiring other concomitant anti-cancer therapies.
- Intercurrent illness that prevents further administration of therapy.
- Patient withdraws consent from the study.
- If deemed in the best medical interest of the patient.
- Protocol violation: Related to protocol specific study procedures, chemotherapy and/or radiotherapy regimen or treatment schedule for the study.

Treatment of patients—dosages and administration:

Chemotherapy:

Nanoparticle paclitaxel was administered at a dose of 80 mg/m² over 1-hour infusion once weekly for 6 weeks, if not tolerated the dose was down-regulated in the multiples of 10 mg/m² as deemed necessary in the best medical benefit of patient. Weekly nanoparticle paclitaxel was given usually at the beginning of the week, 1 hour before radiation treatment. Premedication with antiemetic given before chemotherapy.

Radiotherapy:

The total planned dose of radiation was 60 Gy (over 6 weeks) in 30 fractions of five days per week (2 Gy/daily and then rest for 2 days) for 6 weeks. Patients were treated on a high-energy linear accelerator using a 6 MV photon beam, and irradiation was started on day one.

Concomitant Therapy:

No other therapy was given while the patients were in the study. Any disease progression requiring other forms of specific anti-tumor therapy was discontinued from the study.

Study schedule and evaluations:

The study consisted of three phases:

- Pretreatment (Screening) Phase:
This period was of maximum 14 days (2 weeks), during which screening for the eligibility in study

was performed and pretreatment baseline evaluations were conducted.

- b. Treatment (On Therapy) Phase:
During this phase, patient received active treatment (chemotherapy and radiotherapy) for a period of 6 weeks.
- c. Post Treatment (Follow Up) Phase:
All patients were followed every month for six month and every three months thereafter.

Assessment of efficacy:

All patients were assessed for efficacy as per RECIST Criteria.^{9,10} Tumor measurements for response assessment were done at baseline and one week after treatment. The parameters for evaluating efficacy were:

- a. Clinical examination
- b. Tumor measurements with CT/MRI.

Assessment of safety:

Clinical and laboratory parameters were used for evaluation of safety. The National Cancer Institute common toxicity criteria for adverse events (NCICTCAE, version 3) were used to grade an adverse effect that includes:

- a. Change in physical examination findings.
- b. Change in laboratory evaluations, including serum biochemistry and hematology.
- c. Adverse events (AE) and Serious Adverse Events (SAE).

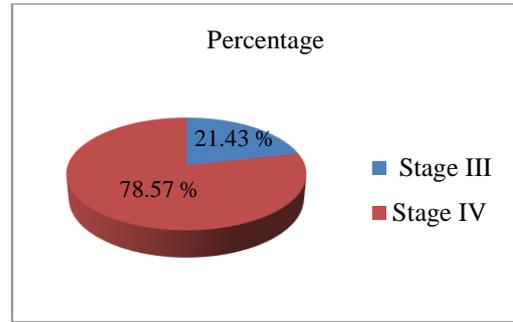


Figure 1: Stage distribution.

RESULTS

All patients of advanced SCCHN treated with concurrent chemo-radiotherapy with weekly nanoparticle paclitaxel were included in study. Patients with progressive disease or dropouts due to toxicity or socio-personal reasons were also included in study to reduce bias.

Total numbers of patients in the study were 28, out of which 6 (21.43%) of stage III and 22 (78.57%) of stage IV. Patient’s characteristics are listed in Table 1.

Efficacy analysis:

Response assessment done six weeks after completion of treatment. RECIST criteria were used for assessing efficacy. Out of 28 patients, 19 (67.86%) patients having immediate response, in which 8 (28.57%) patients with complete response (CR) and 11(39.29%) patients with partial response (PR). One patient was withdrawn from study due to intolerable toxicity in the form of severe mucositis. Eight patients dropped out during treatment.

Table 1: Patient characteristics.

Patient characteristics		Number	Percentage
Patients entered		28	
Median Age		49 Yrs. (range →24-75)	
Sex	Male	19	67.86%
	Female	9	32.14%
Primary Site	CA_Epiglottis	3	10.71%
	CA_Lower_Alveolus	9	32.14%
	CA_Lt_Buccal_Mucosa	1	3.57%
	CA_Lt_Gingivobuccal_Sulcus	2	7.14%
	CA_Lt_Tonsil	1	3.57%
	CA_Rt_Buccal_Mucosa	2	7.14%
	CA_Rt_lateral_border of tongue	7	25.00%
	CA_Rt_Retromolar_Trigone	1	3.57%
	CA_Rt_Upper_Alveolus	1	3.57%
	CA_base_of_Tongue	1	3.57%

On follow up, in patients with CR, one had disease progression at 1.5 year and two at 2 years. All partially

responded patients progressed later. On further follow up at 5 years two patients still having CR, and one patient of

lower left gingiobuccal sulcus had recurrence at floor of mouth right side. Overall objective response rate (ORR) was 67.87% at six weeks, 28.57% at one year, 25% at two years and 10% at 5 year.

Safety analysis:

The National Cancer Institute common toxicity criteria for adverse events (NCICTCAE, version 3) were used to grade an adverse effect.¹¹ The major grade 3-4 toxicity observed were mucositis in 35.7%, skin reaction 25%, xerostomia & dysphagia 14.2% each, trismus and laryngeal oedema in 7% cases. 10.7% have other side effects like anaemia, thrombocytopenia.

DISCUSSIONS

For treatment of advanced SCCHN, RT had been combined with chemotherapy on various studies. Initially, most combinations included once-daily RT combined with cisplatin either alone or with 5-fluorouracil (5-FU). More recently, combinations with twice-daily RT have been reported, but usually with several breaks in the RT schedule due to expected severe mucositis. For example, Brizel et al., despite reduced doses of Cisplatin and 5-FU, were not able to design a tolerable schedule of chemotherapy with twice daily RT without a mandatory treatment break.¹² Staar et al., using twice daily RT with 5-FU and Carboplatin, reported a high incidence of swallowing problems, with a 30% incidence of long-term (2 yrs.) dependency on feeding tubes.¹³ Tishler et al., using docetaxel with once-daily RT after induction with cisplatin and 5-FU, reported an excellent 2-year survival rate but with a 30% incidence of feeding tube dependency, and 24% of their patients required placement of a tracheostomy tube.¹⁴

The treatment of recurrent squamous cell carcinoma of the head and neck with single-agent paclitaxel at a dose of 250 mg/m² every 3 weeks reportedly resulted in a response rate of 40%, making it one of the most active drugs for this disease. Docetaxel, the other Taxane that has been approved for clinical use, has shown similar excellent activity in patients with head and neck carcinoma. Several reports in head and neck carcinoma and other tumor types have suggested that lower weekly doses of paclitaxel may have greater activity with less toxicity than the every 3 week schedule. Taxanes also have favorable radio-sensitizing properties, because they block dividing cells at the G2/M phase, the most radiosensitive part of the cell cycle. Several investigators have tested the tolerability of various doses and schedules of Paclitaxel when used with RT.

We have used newer agent Nanoparticle Paclitaxel in place of normal paclitaxel. Most of the patient remains compliant for this drug because of following reasons:

1. Can be administered on day care basis.

2. Requires less number of drugs and intravenous fluids for pre and post medication.
3. The duration of administration is short.
4. Being formulated in water based vehicle, was well tolerated by patients and was less toxic.
5. Being nanoparticle, selectively targets tumor cells and have longer circulation time, hence more effective.
6. Less costly than other targeted agents used for concurrent chemoradiotherapy for advanced SCCHN.

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