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Nab Paclitaxel and Carboplatin as Induction Chemotherapy in Head Neck Cancer Patients: Efficacy and Tolerability

H.U.Ghori,Vivek Tiwari, O.P.Singh, V.Yogi, Abhishek Shrivastava.
Department of Radiation Oncology, Gandhi Medical College ,Bhopal (M.P.) INDIA.

Abstract : *Background: The objective of this study was to compare the efficacy and tolerability of nab paclitaxel (NP) and carboplatin based induction chemotherapy (IC) for advanced head neck squamous cell carcinoma patients.*

Methods: 32 patients with advanced head and neck cancer who underwent three cycles IC with NP and carboplatin were retrospectively analysed for the response and tolerability.

Results: 28 patients completed the planned course of IC. The number of patients achieving complete response; partial response; stable disease;progressive disease at the primary and neck nodal site were 10/16/2/0 and 7/8/0/1 respectively. The most common adverse effects encountered were fatigue (71%), peripheral sensory neuropathy (53.57%) , Gastrointestinal(32.14%) and anemia (17.85%).

Conclusion: NP- Carboplatin based IC showed response comparable to the literature and with fewer adverse effects. This regimen can be beneficial in high volume centres.

Keywords : *Efficacy, Head and neck cancers, Induction Chemotherapy, Nab-Paclitaxel, Tolerability*

I. INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) is one of commonest malignant tumours, frequently diagnosed in an unresectable advanced stage [1] and 5 year overall survival rates are to the tune of 40-60% [2]. Induction chemotherapy (IC) has been used in the management of advanced HNSCC owing to its advantages of potential organ preservation, early identification of patients likely to benefit from chemo-radiotherapy (CRT), and decreased incidence of distant metastases [3]. The most commonly used IC regimen is docetaxel, cisplatin and 5-flurouracil based and has shown a survival benefit with docetaxel added to cisplatin and fluorouracil [4, 5]. Since taxol is a relatively insoluble compound, polyoxyethylated castor oil (Cremophor®EL) and ethanol are used as solvents to enhance its solubility. Consequently, patients must receive premedication with corticosteroids, antihistamines and histamine-2 receptor antagonists prior to administration of taxols. Despite premedication, approximately 40% patients have been reported to exhibit mild hypersensitivity reactions and almost 3% have serious and life-threatening reactions [6]. Premedication with polyoxyethylated castor oil may also result in peripheral neuropathy and alter the pharmacokinetics of taxols [7].

Nab-paclitaxel (NP) is a soluble form of paclitaxel that is linked to albumin nanoparticles. The development of nanotechnology as a delivery system for paclitaxel has provided better pharmacokinetic and pharmacodynamic characteristics by neutralizing its hydrophobicity [8].

NP is synthesized by a process of high pressure homogenization of paclitaxel in the presence of human albumin and was originally developed to reduce the toxicity usually associated with cremophor in soluble paclitaxel and to increase its penetration in tumour tissues. It is already approved in the first-line treatment of metastatic pancreatic carcinomas and in second line therapy for metastatic breast cancer. In addition, owing to its profile of security and its good tolerance, NP is being tested for many other situations in oncology [9]. The present study reports the clinical experience of HNSCC patients treated with NP at our institute, and describes the initial experience.

II. MATERIAL AND METHODS

Patients-Data regarding 32 patients with advanced HNSCC who received NP in the department of Radiation Oncology, Gandhi Medical College, Bhopal between January 2015and April 2015were retro-spectively analyzed. All the patients had a diagnosis of SCCHN and were evaluated before each cycle for CBP, LFT and RFT. The patients with parameters within normal range were prescribed the IC.

Treatment- NP was administered as a continuous intravenous infusion over the course of 60 min along with inj. Carboplatin every three weeks.

Response and toxicity assessment- Clinical examination and computed tomography (where feasible) were performed at baseline and after three courses to assess the response. The response was assessed clinically after completion of 3 cycles (q21 days) and was categorized as complete response (CR: complete resolution of the primary tumour), partial response (PR: greater than 50% decrease but less than CR), stable disease (SD: 0–49% decrease) or progressive disease (PD: any increase).

Adverse events were evaluated in terms of unacceptable gastrointestinal (nausea/vomiting), hematologic (anemia/neutropenia/thrombocytopenia), deranged LFT/RFT and any neurological or dermatological event requiring active intervention/ hospitalisation.

Counter measures against adverse events- Patients were prescribed post chemo medications that included oral antacids, antiemetics (3 days) and MV/BC capsules along with hematinic syrup (20 days). Any patient who had a TLC count of < 4500/cmm also received a single dose of inj. Filgrastim 300 microgram s/c a day after the chemotherapy.

III. RESULTS

Patient characteristics: (Table 1) 32 patients with loco regionally advanced histopathology proven HNSCC were evaluated retrospectively. Total number of males was 23 (71.9%) while females were 9 (28.1%). Mean age was 45.04 years in males (range: 20-65 years) and 49 years in females (range 38-62 years). 27 patients (84.37%) had large (T3, T4) primary tumours and 18 patients (56.25%) had bulky (>N2b) nodal disease in the neck. The most common site of malignancy was oral cavity (17/32), followed by oropharynx (9/32) and larynx (6/32) .The average duration of symptoms was 4.5 months (range: 3-15 months).

Treatment characteristics: 28/32 (87.5%) patients completed the prescribed course of IC. 4/32 (12.5%) patients did not complete the treatment out of which one patient expired after the first cycle due to excessive bleeding from the primary site while remaining three defaulted midway during the treatment. These patients were not considered for further assessment.

Primary tumour response to IC: (Table 2) Of the 28 patients who completed 3 courses, 10 patients (35.57%) achieved CR, 16 patients (57.1%) achieved PR while two patients (7.14%) persisted with a SD. No patient showed progression of the primary disease during the course of IC.

Neck nodal response to IC: (Table 2) The tumour response rates at neck nodal sites after completion of the prescribed course were CR in 7 patients (43.75%) and PR in 8 patients (50%). One patient (6.25%) showed a PD despite a PR at the primary site.

Adverse events during/after IC: (Table 3) The adverse events encountered were of low grade and constituted mainly of fatigue (71%), peripheral sensory neuropathy in the form of lower limb pain (53.57%) and gastrointestinal (nausea/vomiting or diarrhoea) (32.14%). We also encountered asymptomatic neutropenia (25%, most likely carboplatin induced). A fall in the Haemoglobin level was seen in 17.85% patients towards the 3rd course but remained within acceptable range. One patient (3.57%) developed cough and fever but responded to a course of oral antibiotics. There were no events comprising of skin reaction, oral mucositis, vomiting or diarrhoea.

IV. FIGURES AND TABLES

Table 1Patient Characteristics

	N	Percentage
Total number of patients	32	100
Males	23	71.9
Females	09	28.1
SITE		
Oral cavity	17	53.12
Oropharynx	09	28.12
Larynx	06	18.75

Table 2: Treatment response

PRIMARY TUMOUR		
	N	Percentage
CR	10	35.57
PR	16	57.1
SD	02	7.14
PD	00	00
NECK NODAL DISEASE		
CR	07	43.75
PR	08	50
SD	00	00
PD	01	6.25

CR= complete response; PR=partial response; SD=stable disease; PD=progressive disease.

Table 3: Adverse effects encountered during Induction Chemotherapy

	N	Percentage
Infusion reaction	00	00
Fatigue	20	71
Dermatologic manifestation	00	00
Mucositis	00	00
Nausea/vomiting/diarrhoea	09	32.14
Anemia	05	17.85
Neutropenia	07	25
Thrombocytopenia	00	00
Febrile neutropenia	00	00
Infection	01	3.57
Peripheral sensory neuropathy	15	53.57

V. DISCUSSION AND CONCUSION

HNSCC is the most common subtype of cancer in adult males in India and the leading cancer site among males at our department. The routine recommendation for treatment of locally advanced HNSCC is surgical management of the primary tumour and neck followed by post-operative radiotherapy or chemo-radiotherapy depending on the presence of intermediate/high risk features [10]. The use of IC prior to definitive treatment for management of locally advanced HNSCC is under continuing research and in clinical trials TAX323 and TAX324, (which investigated non-surgical management of HNSCCs) , IC with docetaxel, cisplatin and 5-fluorouracil (TPF) has been found to improve survival compared to induction cisplatin and 5-fluorouracil [11]. Recent studies have also reported an improvement in overall survival (OS) in patients treated with induction TPF followed by concurrent chemo-radiotherapy compared to concurrent treatment upfront [11]. In addition, the novel induction regimen including NP has been found to be feasible and has resulted in a high CR rate at the primary tumor site even in large (T3,4) primary tumours [12].

This study aimed at understanding the tolerability and response of NP to the cohort of patients catered in our department. CR at the primary tumour site as assessed by clinical examination following IC is a favourable predictive factor for OS and disease-control in patients with HNSCC subsequently treated with definitive RT [13, 14].

Compared with conventional preparations of paclitaxel, NP has a number of advantages: i) No premedication to prevent hypersensitivity is required; ii) any type of intravenous infusion set may be used (with no requirement for in-line filters); iii) nab-paclitaxel may be used even in patients who are sensitive to alcohol; and iv) NP may be administered at a higher dose over the course of a shorter time period than paclitaxel [15].

In this study we found 35.57% CR rate at the primary tumour site following three cycles of the prescribed IC. These data compare favourably to the likelihood of achieving a CR at the primary site and in accordance with literature: 21% in laryngeal HNSCC [16], 20% in oropharyngeal carcinoma [17], and 33% in oral cavity carcinoma [18].

SPARC (secreted protein acidic and rich in cysteine) plays a role in albumin receptor mediated

endothelial transport [19]. SPARC expression is common in tumour and stromal cells of HNSCC but not in adjacent normal oral mucosa [20] and correlates with tumour response to NP in HNSCC [21]. In addition, macropinocytosis, the process by which macromolecules like albumin are taken up into cells, is up regulated in the setting of activated RAS or PI3K pathways [22]. RAS and/or components of the PI3K pathways are frequently activated in HNSCC [23] are a few postulates explaining the high anti-tumor effect of NP in HNSCC.

We did not observe even a single grade 3 adverse effect during the course of the IC requiring hospitalisation. All the expected side effects (nausea, vomiting, fall in blood count) were minimal and avoided using simple post chemotherapy medication empirically. The most frequent complaint of fatigue (71%) and lower limb pain (53.57%) responded to symptomatic treatment. In comparison, literature review shows reported rates of > grade 3 adverse reactions with induction TPF to be 27-85% , 77% with induction Docetaxel, cisplatin and Cetuximab and 45 % with weekly paclitaxel, carboplatin and cetuximab [24-26].

NP along with carboplatin appears to be a safe, well tolerated and efficient regimen for IC in advanced HNSCC patients. With the advantages of no premedication, relative ease of administration, acceptable side effects and at par response with the conventional regimens, its use can be of much benefit to large volume centres. NP has thus overcome the predominant disadvantages of paclitaxel, and exerts enhanced antitumor activity. However, larger studies with detailed analysis are advocated.

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