International Journal of Endorsing Health Science Research
Int. j. endorsing health sci. res.
Published by Advance Educational Institute and Research Centre

IJEHSR

Original Article

Vinorelbine as a radiosensitizer in Pakistani patients with locally advanced unresectable head & neck cancer (HNC) in tertiary care hospital of Pakistan

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DOI:10.29052/IJEHSR.v7.i3.2019.116-123

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Received 07/03/2019
Accepted 26/07/2019
Published 01/09/2019

Abstract

Background: Head and neck cancer (HNC) is one of the most common cancers in Pakistan. Disease free survival in HNC remains poor due to inefficient loco-regional disease control. The aim of the present study was to assess the response rate and toxicity of concomitant vinorelbine and External radiation therapy (ERT) in advanced Head and Neck cancer in local Pakistani population. The study as per Good Clinical Practice (GCP) guidelines was conducted at the oncology department of Nishat hospital Multan from 2015 to 2017.

Methodology: An observational, prospective study with enrolment of 50 patients of advanced head and neck cancer was followed to analyze the outcome for radiosensitization. Primary tumor sites were tongue in 15 (30%) patients; lower lip in 6 (12%); buccal cavity in 5 (10%); cheek in 5 (10%); tonsil in 4 (8%); larynx in 6 (12%); hypopharynx in 5 (10%); and parotid in 4 (8%) patients. Initial clinical stage was: IV in 23 (46%) patients and III in 27 (54%) patients. Vinorelbine (VNB) was given at dose of 10 mg i.v. infusion weekly with ERT (3D conformal radiation plan). Response rate was evaluated after at least 8 doses. Response evaluation criteria in Solid Tumors (RECIST) was used to assess complete response (CR) and partial response (PR); progressive disease (PD) and stable disease (SD). Toxicity was assessed using common toxicity criteria version 3.0 (CTCV3.0).

Results: 44 out of 50 patients were evaluable for response rate and toxicity. Immediate response was 90% CR. After 24 months of followup CR, PR, SD, and PD were seen in 26 (59%), 6 (13%), 7 (15%) and 6 (13%) patients respectively. Grade III mucositis and dysphagia were observed in 19 (43%) and 8 (18%) patients respectively, grade III skin rash in 14 (30%) patients, grade-II peripheral neuropathy was seen in 3 (6%) patients.

Conclusion: The study showed that vinorelbine as a radiosensitizer in advanced HNC is a feasible option with acceptable toxicities. A large study is required to define its definite role.

Keywords

Locally advanced Head & Neck Cancer, Vinorelbine, External radiation therapy

Introduction

Head and neck cancer (HNC) is one of the most common tobacco-related cancers worldwide[1], and squamous cell carcinoma is ninety percent (90%) of all HNC. The majority of patients presented with, advanced primary and node involving disease (stage III—IVB) according to Tumour Node Metastasis (TNM) classification.

The long-term prognosis of patients with advanced HNC has been poor, not only because of metastatic disease, but also primarily because of failure in locoregional disease control[2]. The primary treatment of head & neck squamous cell carcinoma (HNSCC) is surgery and radiotherapy. The use of concurrent chemo radiation has been clinically investigated since 1960s. The simultaneous administration of chemotherapy and radiotherapy aimed at improving both systemic and loco-regional tumor control[3]. Most of the studies throughout the 70s and 80s have been focused on the use of single-agent chemotherapy during a standard course of single daily fraction radiotherapy[3-5]. The single agents most frequently used were Methotrexate, Bleomycin, Mitomycin-C, 5-Fluorouracil and Cisplatin. The use of multiagent chemoradiotherapy has also been studied in patients with advanced HNSCC[6].

Vinorelbine is a unique semisynthetic vinca alkaloid that differs from the naturally occurring compounds, vinblastine and vincristine, in its chemical structure, selectivity for mitotic microtubules and toxicity profile[7]. Vinorelbine is a classic anti-tubulin in that its mechanism of action involves arresting mitosis at metaphase by binding to tubulin, leading to the inhibition of tubulin assembly and microtubule formation[8]. Thus, it is a cell-cycle-dependent antimitotic agent blocking progression in the G2/M cell phase, which is the most sensitive phase of the cell cycle to irradiation. Clinical studies showed relatively few side effects and neutropenia as the dose-limiting toxicity of vinorelbine. Since vinorelbine has relatively low affinity for axonal microtubules compared to other mitotic inhibitors, its neurotoxicity is mild[9]. Vinorelbine has shown a broad spectrum of activity against breast cancer, lung cancer, ovarian cancer and lymphoma[10-12]. Currently, vinorelbine is in routine clinical use against breast and lung cancer. In vitro studies showed that vinorelbine is able to potentiate the antitumor effects of radiation in non-small cell lung cancer[13]. Furthermore, clinical studies have proved that vinorelbine is a promising radiosensitizer in locally advanced non-small cell lung cancer[14].

In vitro study has shown that HNSCC cells are constantly sensitive to vinorelbine[15]. A pilot study on vinorelbine as radiosensitizer in HNSCC & esophageal SCC has shown excellent results with less toxicity[16]. In this phase II study, we evaluated the response and toxicity of vinorelbine as a radiosensitizer in HNSCC. The current single centre study assesses the response rate and toxicity of concomitant vinorelbine and ERT in advanced HNC in local Pakistani population.

Methodology

This was an observational, prospective, single-centre study conducted at the department of radiotherapy and oncology, Nishtar hospital, a leading tertiary health care facility in Multan, Pakistan. The study conducted as per GCP guideline and approved by an institutional review board. Patient's selection: The eligibility criteria included histologically confirmed locally advanced HNSCC, stage III & IVa. Patients were required to be between 30 and 75 years old, to have a performance status (WHO) ≤2. No chemotherapy or other treatment was given, normal bone marrow function with normal hepatic and renal function at the start of treatment, and to give informed written consent. Early stage patients

were excluded, as it shows good response to surgery or radiation alone. Patients with distant metastatic disease, previously treated patients, poor performance status having severe anaemia, hepatic and renal dysfunction were also excluded.

Treatment: Vinorelbine was administered at a dose of 10 mg weekly. Patients were treated by short-duration i.v. infusion. The patients received vinorelbine until occurrence of unacceptable toxicity. Evaluation during therapy included; weekly physical examination and vital signs, complete blood counts on day 7 of each cycle, before the start of the next cycle of treatment; and monthly measurement of serum electrolytes, hepatic and renal function profiles. If during treatment the neutrophil count was < 1.0 x 109 and / or platelets < 100 x 109 or any other toxicity > grade 3, administration of the vinorelbine was delayed until toxicity settled. The ERT was delivered with 3DCRT using 6MV energy with weekly vinorelbine, 2.0Gy per day upto 70 Gy. Evaluation of response and toxicity: RECIST was used to assess CR, PR; PD and SD[17]. Toxicity was assessed using CTCV3.0. A first assessment was performed after eight weeks of treatment and then every eight weeks or as indicated by new symptoms. The patients with complete radiologic response and with microscopic disease on endoscopic biopsies were considered to be in partial remission. All radiological examinations and CT scans were reviewed by an independent radiologist and all tumor responses were confirmed by an investigator's panel discussion.

Results

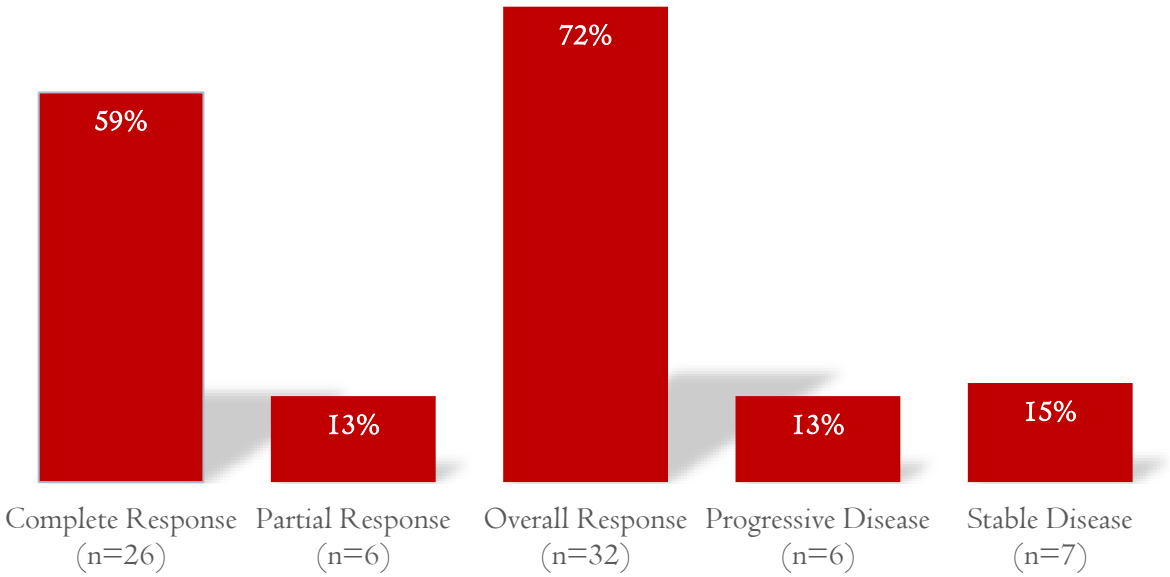
In two years period from March 2015 to June 2017, as per the inclusion/exclusion criteria, 50 patients with confirmed locally advanced HNSCC (stage III & IVa) were recruited. In the study, the majority of the patients were male (n=34, 68%), the primary site was mainly oral cavity 27(54%). After twenty four months of follow up, 3 deaths were documented and 3 patients were lost to follow-up. The patient's characteristics details are mentioned in Table I

Table I: Patient related characteristics (Gender, age, performance status, primary site)

Patient Characteristics	(n=50)
Male	34(68)
Female	16(32)
Age	56±30-75 (Median, Range)
Performance Status	
0	13(26)
1	21.5(43)
2	15(30)
Site Involved	
Oral cavity	27(54)
Oropharynx	05(10)
Hypopharynx	04(8)
Larynx	11(22)
Parotid	03(6)

*Values are given as n(%)

Figure 1: Tumor Response to Treatment



Efficacy

Among the 44 patients evaluable for tumor response, there were twenty six (59%) CR and six (13%) (PR, for overall response rate (OR) of 72%. (Figure: 1) Taking in account all 50 of eligible patients, overall response rate was 64%. Twenty six complete tumor responses were confirmed by radio-logically disappearance of the disease. Two cases of PR (Tongue) achieved CR after 8 more cycle of vinorelbine, weekly (DFI: 16 months). One case of post cricoid showed PR and after giving 6 more cycle of vinorelbine that achieved CR (DFI: 18 months). Seven patients (15%) had SD, and six patients (13%) had PD and three deaths were documented during follow up.

Toxicity Profile

Forty seven patients were evaluable for toxicity using CTCV 3.0, summarized in table 2. Hematological toxicity was not seen in these patients, only grade-I anaemia was observed during treatment which was corrected by blood transfusion and growth factors were not given in this study. Grade-III mucositis and dysphagia was seen in 19 (43%) and, 8 (18%) patients respectively, which was radiation induced toxicity and was corrected by chlorhexidine lozenges for mucositis with antifungal prophylactically, and i.v. alimentation and antacids for dysphagia. Grade-III skin rash was seen in 14 (30%) patients, local emollient ointments were used for this. Grade-II peripheral neuropathy was seen in only 3 (6%) patient that was vinorelbine toxicity it was not too severe to delay the treatment. Acute pain at oral and orpharyngeal tumor site was occurred in 20 (40%) patients and required morphine therapy during treatment. Nausea and vomiting were infrequent. Anorexia was more common flu like symptom.

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Table 2: Grade of Toxicity (Reported Adverse Events)

Toxicity	Grade I	Grade II	Grade III	Grade IV
Mucositis	11(25)	20(45.4)	19 (43)	__
Dysphagia	26(59)	13(29.5)	8(18.1)	--
Skin rash	26(59)	10(22.7)	14(31.8)	__
Neuropathy	21(47.7)	2(4.5)	__	__
Nausea & vomiting	29(66)	__	3(13.6)	__
Acute pain	18(41)	12(27.2)	20(45.4)	__
Anaemia	22(50)	4(9)	3(6.8)	-
Anorexia	23(52.2)	13(29.5)	6(13.6)	__

*Values are given as n(%)

Discussion

The prognosis for patients with advanced HNSCC remains poor. Chemotherapy has been used extensively in these patients. Many anticancer drugs have been identified as active in patients with advanced HNSCC. Methotrexate, cisplatin, carboplatin, bleomycin and 5-fluorouracil (5-FU) are the most efficient cytotoxic agents commonly used in patients with advanced HNSCC. Among the new drugs, paclitaxel and docetaxel have demonstrated the most promising activity in these patients. The overall response rates to each of these cytotoxic agents ranges between 10% to 40% in phase II studies but more recent randomized trials reported the overall response rates less than 20% for methotrexate, cisplatin and 5-FU. Treatment with combination chemotherapy results in higher response rates than single agents (30%-40% vs. 10%-20% respectively) without clearly improving survival; complete responses are rare, duration of responses is usually short (four to six months) and the median survival is approximately 6 month[17-25].

The results of our phase II study suggest that vinorelbine is an active drug in locally advanced HNSCC. In this study of 44 evaluable patients, the overall response rate was 72% with 26 CR and 6 PR, and median duration of response was 5 months. Our results appear comparable to the pilot study of vinorelbine as radiosensitizer in HNSCC and esophageal cancers published by Shudarshan and mahadev[26]. In 25 out of 30 cases (83%) were alive with no disease, but this included both of HNC and esophageal cancer, in which 16(64%) were of esophageal cancer and 9(36%) were of HNC with recurrence in HNC. But in our study response rate of HNSCC was 72%, which is comparable with that pilot study, 36%. Many studies have been done using vinorelbine in recurrent or metastatic HNSCC, with low profile of overall response rate[27&28]. For the first time, we have used vinorelbine as radiosensitizer in locally advanced HNSCC with comparable results.

The main toxicities observed ware mucositis and dysphagia which were mainly due to radiation and didn't cause treatment delay. Neurotoxicity was mild, because, tubulin binding at low dose (10mg) causes minimal effect on axonal microtubules leading to decreased neurotoxicity. No neutropenia observed in our study, grade I anaemia was seen which could be managed symptomatically.

The dose intensity of vinorelbine in this study was 10 mg weekly. Regarding the observed tolerance (grade III mucositis and dysphagia) and this dose intensity, the chosen dose of

vinorelbine, 10 mg weekly with radiation, seems to be optimal dose for this population.

Conclusion

In conclusion, vinorelbine is a drug with documented antitumor activity and acceptable toxicity at the dose and schedule administered in this study in patients with locally advanced HNSCC. The favourable toxicity profile of vinorelbine, its demonstrated efficacy and possible therapeutic synergy with other drugs and/or its radio sensitizing effect offer opportunities for ongoing and future development of vinorelbine.

Conflicts of Interest

This to be declare that all authors have no significant competing financial, professional or personal interest that might have influenced the performance of data collection, manuscript writing or submission.

Acknowledgement

The authors are thankful to the entire team involved in this study and we appreciate their support throughout the study.

Funding

None.

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