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Main Article

Comparative study of efficacy and toxicities of cisplatin *vs* vinorelbine as radiosensitisers in locally advanced head and neck cancer

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Abstract

Introduction: Currently, concomitant chemoradiation using cisplatin is one of the standards of care for the management of head and neck cancer, but at the cost of increased acute toxicity. Our aim was to assess whether vinorelbine was less toxic and of at least comparable efficacy, if not better, compared with cisplatin.

Materials and methods: A total of 72 patients with squamous cell carcinoma in the head and neck region were recruited, 40 in arm A and 32 in arm B. Patients in arm A received 40 mg/m^2 cisplatin weekly. Patients in arm B received 6 mg/m^2 vinorelbine weekly. Both arms also received 66 Gy of radiation in conventional fractionation.

Results and analysis: There was no statistically significant difference in response rate or toxicities between the two arms, except for nausea and/or vomiting, which was significantly less frequent in the vinorelbine arm.

Conclusion: Vinorelbine was as effective as cisplatin in controlling locoregional disease in locally advanced head and neck cancer, but was only marginally less toxic than cisplatin.

Key words: Chemoradiation; Head and Neck Cancer; Toxicity, Concomitant

Introduction

In locally advanced head and neck cancer, long-term survival following any form of radiation treatment (including three-dimensional conformal therapy and various altered fractionation schedules) is currently poor; the disease-free survival rate is only 30–40 per cent. Locoregional failure is the predominant pattern of failure (local control rates of up to 70 per cent).[1]

Concomitant chemoradiation is one way of improving local control and long-term survival. Pignon and colleagues showed, in a meta-analysis including 3727 patients, an absolute survival advantage of 8 per cent at five years, but at the cost of increased toxicity.[2] Increased toxicity is the main problem with concomitant chemoradiation therapy, as shown in several studies.[3,4]

However, very few single-agent chemoradiotherapy regimens have undergone head-to-head comparison in randomised clinical trials. Therefore, no optimal regimen has yet been defined. To date, cisplatin-based concomitant chemoradiotherapy remains the most widely used and efficacious regimen.[5]

In our search for a new drug with an acceptable toxicity profile, we have already performed a pilot study using vinorelbine (a vinca alkaloid), a cell cycle specific drug that prevents the assembly of microtubules during mitosis, leading to abnormal mitosis and cell cycle arrest in the G2-M phase. Since the G2-M phase is the most radiosensitive period of the cell cycle, theoretically vinorelbine should be a potential radiosensitiser. Our pilot study with vinorelbine showed favourable results. Following this, we performed the current, comparative study of cisplatin *vs* vinorelbine as radiosensitisers in the treatment of locally advanced head and neck cancer, assessing local response and toxicities.

The aims and objectives of this study were to ascertain: (1) whether vinorelbine was better tolerated than cisplatin as regards both acute and late toxicities; and (2) whether the response rate for vinorelbine was at least comparable with, if not better than, that for cisplatin.

Materials and methods

The present study was conducted in the department of radiotherapy, Medical College Hospital, Kolkata, from January 2005 to January 2006.

Patient inclusion criteria

Patients with the following characteristics were included in the study: biopsy-proven squamous cell

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carcinoma of the head and neck, of stage III or IV (non-metastatic); normal liver, kidney and bone marrow function; no prior history of anti-cancer therapy; good performance status (Karnofsky performance score >70); not pregnant; age <70 years; and informed consent supplied.

Study protocol

Patients were randomised into two arms, A and B.

In arm A ($n = 40$), patients received 66 Gy of radiation in 33 fractions over six and a half weeks via a Telecobalt machine (Theratron 780C, Theratronics International, Canada), using conventional methods. Patients also received weekly concomitant chemotherapy with 40 mg/m^2 cisplatin via intravenous (IV) infusion.

In arm B ($n = 32$ patients), patients received the same dose of external beam radiation (EBRT) as above, along with weekly concomitant chemotherapy with 6 mg/m^2 vinorelbine via slow IV injection.

In both arms, patients were reviewed weekly during chemoradiation, and toxicities were monitored and recorded at each review using European organization for the research and treatment of cancer (EORTC)/ Radiation therapy oncology group (RTOG) criteria.

Follow up

Patients were reviewed at the end of chemoradiation and assessed for disease response and toxicities. Patients were then followed up at monthly intervals for six months and at two monthly intervals thereafter. At the time of writing, at least six months' follow-up data had been recorded for all patients.

Results and analysis

Between January 2005 and January 2006, 72 eligible patients entered the study. Of these, 40 entered arm A and 32 entered arm B. All patients were evaluated for toxicity and response.

The clinical characteristics of these patients and their tumours are presented in Table I.

TABLE I

PATIENT AND TUMOUR CHARACTERISTICS

Characteristics	Patients (*n*)	
	Arm A*	Arm B†
Sex		
Male	32	26
Female	8	6
Age (years)		
<45	2	1
45–55	8	13
55–65	29	15
>65	1	3
Site		
Oropharynx	12	6
Hypopharynx	10	11
Larynx	16	14
Other	2	10
Stage		
III	23	19
IV	17	13
Nodal status		
Positive	27	20
Negative	13	12

*$n = 42$; †$n = 32$. Arm A = cisplatin; arm B = vinorelbine

Local response

Local responses at the end of treatment are shown in Table II.

In arm A (cisplatin), out of 40 patients, 29 (72.5 per cent) achieved a complete response, while 11 (27.5 per cent) achieved only a partial response. Thus, the overall response rate was 100 per cent.

In arm B (vinorelbine), out of 32 patients, 23 (72 per cent) achieved a complete response, while nine (28 per cent) achieved a partial response. Here again, the overall response rate was 100 per cent.

The difference in complete response between the two arms was not statistically significant ($p = 0.837$, odds ratio = 1.032, 95 per cent confidence intervals (CI) = 0.323 to 3.282).

The difference in partial response between the two arms was also not statistically significant ($p = 0.837$, odds ratio = 0.969, 95 per cent CI = 0.305 to 3.095).

Of those patients achieving a partial response, three (out of 11) in arm A (cisplatin) and two (out of nine) in arm B (vinorelbine) showed disease progression at six month follow up.

Of those patients achieving a complete response, two out of 29 in arm A (cisplatin) and one out of 23 in arm B (vinorelbine) had disease recurrence at 12 month follow up.

Acute toxicities

Cases of acute toxicity during treatment are shown in Table III.

Dermatitis. In arm A (cisplatin), 27 patients (67.5 per cent) suffered dermatitis of grade one severity, while 13 (32.5 per cent) suffered grade two dermatitis (Figure 1). No case of grade three dermatitis was recorded.

In arm B (vinorelbine), 23 patients (72 per cent) suffered grade one dermatitis, while nine patients (28 per cent) suffered grade two dermatitis. No case of grade three dermatitis was recorded.

There was no statistically significant difference in dermatitis toxicity grading between the two arms ($p = 0.886$, odds ratio = 0.813, 95 per cent CI = 0.26 to 2.51).

Mucositis. In arm A (cisplatin), 17 patients (42.5 per cent) had grade one mucositis and 13 (32.5 per cent)

TABLE II

RESPONSE TO TREATMENT

Response	Arm A* (*n* (%))	Arm B† (*n* (%))
Complete	29 (72.5)	23 (72)
Partial	11 (27.5)	9 (28)

*$n = 40$; †$n = 32$. Arm A = cisplatin; arm B = vinorelbine

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TABLE III
TREATMENT-RELATED TOXICITIES

Toxicity	Arm A* (*n* (%))	Arm B† (*n* (%))
Dermatitis		
Grade 1	27 (67.5)	23 (72)
Grade 2	13 (32.5)	9 (28)
Grade 3	0	0
Mucositis		
Grade 1	17 (42.5)	19 (59)
Grade 2	13 (32.5)	9 (28)
Grade 3	10 (25)	4 (13)
Dysphagia		
Grade 0	0	0
Grade 1	19 (47.5)	19 (59)
Grade 2	21 (52.5)	13 (41)
Grade 3	0	0
Nausea &/or vomiting	25 (62.5)	4 (12.5)
Neutropenia	4 (10)	2 (6)

*$n = 40$; †$n = 32$. Arm A = cisplatin; arm B = vinorelbine

had grade two mucositis (Figure 2). Ten patients (25 per cent) had grade three mucositis.

In arm B (vinorelbine), 19 patients (59 per cent) had grade one mucositis and nine (28 per cent) had grade two mucositis. Four patients (13 per cent) had grade three mucositis.

The differences in mucositis toxicity grading between the two arms were not statistically significant ($p = 0.38$, odds ratio = 2.33, 95 per cent CI = 0.57 for grade three mucositis).

Dysphagia. In arm A (cisplatin), 19 patients (47.5 per cent) had grade one dysphagia and 21 (52.5 per cent) had grade two dysphagia (Figure 3). No patient had grade zero or grade three dysphagia.

In arm B (vinorelbine), 19 patients (59 per cent) had grade one dysphagia and 13 (41 per cent) had grade two dysphagia. No patient had grade zero or grade three dysphagia.

The differences in dysphagia toxicity between the two arms were not statistically significant ($p = 0.444$, odds ratio = 0.62, 95 per cent CI = 0.26 to 1.75).

Nausea and/or vomiting. In arm A (cisplatin), 25 patients out of 40 (62.5 per cent) had nausea and/or vomiting, compared with four out of 32 patients

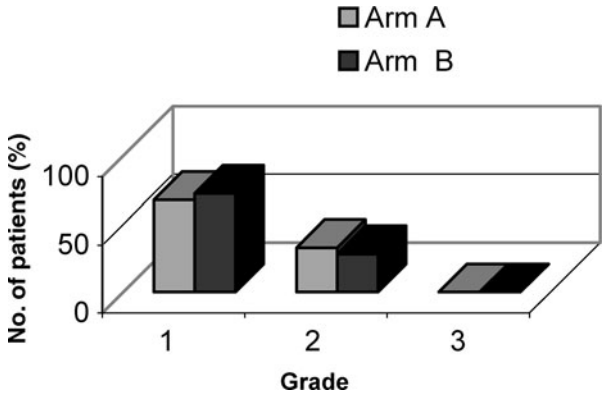

FIG. 1
Dermatitis in arm A (cisplatin) and arm B (vinorelbine).

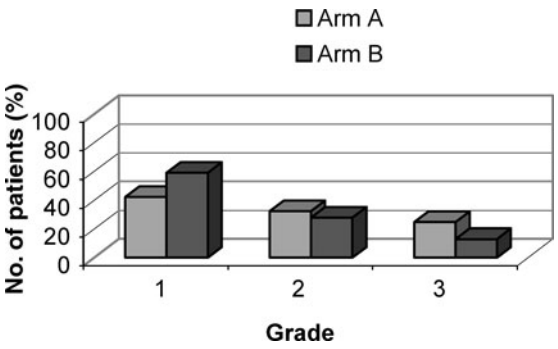

FIG. 2
Mucositis in arm A (cisplatin) and arm B (vinorelbine).

(12.5 per cent) in arm B (vinorelbine) (Figure 4). This difference achieved statistical significance ($p < 0.01$, odds ratio = 15.83, 95 per cent CI = 4.214 to 65.104).

Neutropenia. In arm A (cisplatin), four patients out of 40 (10 per cent) experienced neutropenia, compared with two out of 32 (6 per cent) in arm B (vinorelbine) (Figure 5). The difference between the two arms was not statistically significant.

Discussion

For the treatment of head and neck cancer, synchronous chemoradiation is preferable to sequential chemotherapy and radiation therapy from a theoretical standpoint, in terms of addressing the issue of accelerated repopulation.

Many randomised trials[6–14] and meta-analyses of clinical trials[2,15,16] have demonstrated significantly improved local control, disease-free survival and overall survival for concomitant chemotherapy and radiation therapy, compared with radiotherapy alone.

Several drugs have been used in concomitant chemoradiotherapy treatment protocols for advanced head and neck squamous cell carcinoma. In clinical trials, single agents such as methotrexate, 5-fluorouracil, bleomycin and mitomycin C have shown improved results, compared with radiotherapy alone.[4,6,17]

Currently, the drug most frequently used as a radiosensitiser in patients with head and neck cancer is cisplatin. Almost all studies to date have

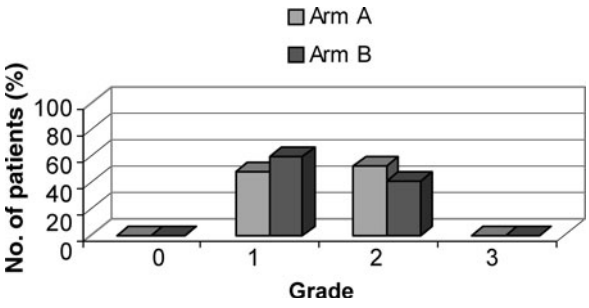

FIG. 3
Dysphagia in arm A (cisplatin) and arm B (vinorelbine).

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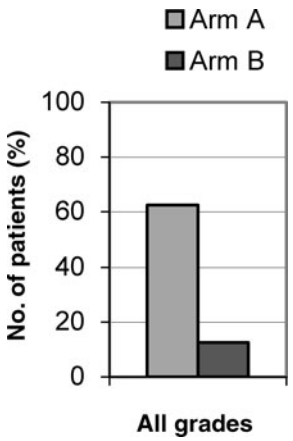

FIG. 4
Nausia and/or vomiting in arm A (cisplatin) and arm B (vinorelbine).

shown an improved local response and survival, albeit at the cost of increased toxicity, including studies with cisplatin and radiation therapy.[2,15,16]

In the search for an alternative drug with acceptable toxicity, we perfomed a pilot study using vinorelbine concomitantly with radiation therapy in 16 patients with advanced head and neck cancer. In that study, we found vinorelbine to be a drug with acceptable toxicity and a considerable response rate.

As an extension of that study, we then attempted to compare the results of vinorelbine and cisplatin as radiosensitisers, with respect to toxicity profile and response rate.

In our study, the response rate was similar in both arms (72.5 per cent *vs* 72 per cent complete response); these results were quite similar to those of other investigators.

Most of the failures were at nodal sites, both for residual disease and for recurrence after complete response.

Toxicities were greater in both arms than in historical patients treated with radiotherapy alone. However, although mucosal toxicity and dysphagia were more frequent in the cisplatin arm, the differences were not statistically significant. Grade three mucosal toxicity and dysphagia occurred more frequently in the cisplatin arm.

- **Concomitant chemoradiation using cisplatin is one of the standards of care in patients with head and neck neoplasms**
- **This study aimed to assess whether vinorelbine was less toxic and of at least comparable efficacy with, if not better than, cisplatin**
- **Seventy-two patients with squamous cell carcinoma of the head and neck region were recruited into the study**
- **Vinorelbine was as effective as cisplatin in controlling locoregional disease in locally advanced head and neck cancer but was only marginally less toxic than cisplatin**

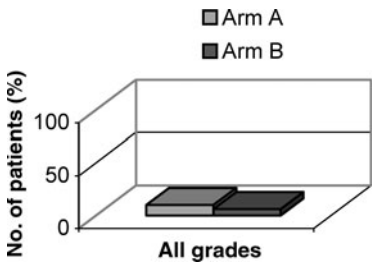

FIG. 5
Neutropenia in arm A (cisplatin) and arm B (vinorelbine).

The only difference in the two drugs' toxicity profiles which achieved statistical significance was that for nausea and/or vomiting (62.5 per cent in the cisplatin arm *vs* 12.5 per cent in the vinorelbine arm, $p < 0.01$). Therefore, we conclude that vinorelbine appears to be as effective a radiosensitiser as cisplatin, in terms of improving the response rate in locally advanced squamous cell carcinoma of the head and neck region. Vinorelbine also appeared to be better tolerated than cisplatin, in terms of acute toxicities.

Therefore, in this preliminary study, vinorelbine appeared to be an acceptable alternative radiosensitiser to cisplatin, in the setting of locally advanced squamous cell carcinoma of the head and neck region. However, the study needs to be continued in order to accrue a larger sample size and thus to obtain statistically significant observations.

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