

A phase I/II dose escalation study of OncoVEX^{GM-CSF} and chemoradiotherapy in untreated stage III/IV squamous cell cancer of the head and neck

K. Harrington, M. Hingorani, M. Tanay, J. Matthews, K. Newbold, L. Renouf, H. Goldswieg, I. McNeish, R. S. Coffin, C. Nutting

Royal Marsden Hospital, London, United Kingdom; Institute of Cancer Research, London, United Kingdom; Barts and The London Hospital, London, United Kingdom
BioVex Inc, 34 Commerce Way, Woburn, MA 01801

Abstract

Background: OncoVEX^{GM-CSF} is a gene deleted (ICP34.5-/ICP47-) oncolytic HSV-1 that encodes human GM-CSF. OncoVEX^{GM-CSF} causes direct oncolytic tumor cell destruction and immune activation by releasing tumor antigens and GM-CSF, effects that may co-operate with CRT to increase loco-regional control in SCCHN.

Methods: Patients: Stage III/IVA SCCHN, N1-N3, ECOG 0-1, normal haematologic, biochemical, immune function. Patients received CRT (70 Gy/35 fractions with concomitant cisplatin 100 mg/m² (day 1, 22, 43) and dose-escalating (10⁶, 10⁷, 10⁸, 10⁹ pfu/ml [cohort 1]; 10⁶, 10⁷, 10⁸ pfu/ml [cohort 2]; 10⁶, 10⁸, 10⁹ pfu/ml [cohort 3]) OncoVEX^{GM-CSF} by intratumoral injection (day 1, 22, 43, 64). Patients underwent neck dissection 6-10 weeks after CRT. Primary objectives were to assess safety and to identify the dosing schedule for future study. Secondary objectives were to assess anti-tumor activity, viral replication and HSV antibody levels.

Results: 17 patients were treated, 9 at the top dose (15 males, median 58 years). DLT and MTD were not reached. There were no delays to CRT delivery. 13 patients had PR or CR by CT, 5 patients achieving rapid CR following only 2 or 3 viral doses. Pathological CR was observed in 94% of patients at neck dissection. Transient low level injection site viral shedding was seen in 3 patients. HSV was detected in injected and adjacent uninjected tumors by qPCR and immunohistochemistry, including at levels higher than the input dose, indicating replication. All seronegative patients seroconverted. No patients had local relapse, 1 patient had a new primary tumor, 3 patients distant metastatic disease, and 2 patients intercurrent disease.

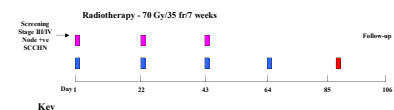
Conclusions: OncoVEX^{GM-CSF} combined with cisplatin-based CRT is well tolerated in patients with SCCHN. Viral replication was confirmed. Long-term loco-regional control was achieved in 100% of patients, 70.5% of patients remaining alive and in complete remission, including two patients who died of intercurrent disease. A pivotal Phase 3 study is being planned.

Introduction

SCCHN is the sixth commonest cancer worldwide. Locally advanced disease (stage III/IV) requires a multidisciplinary approach usually involving radiotherapy with concomitant chemotherapy (CRT). In patients with bulky cervical nodes at presentation, CRT is often followed by neck dissection. Even with such intensive treatment, up to 50% of patients develop loco-regional disease recurrence. OncoVEX^{GM-CSF} is a conditionally replication competent herpes simplex type-1 virus which is currently being tested in a pivotal Phase 3 study in Stage III/IV melanoma. The virus has deletions of ICP34.5, providing tumor selective replication, and ICP47, which promotes antigen presentation, and expresses GM-CSF. OncoVEX^{GM-CSF} has two mechanisms of action: (i) direct destruction of tumor cells through viral replication, and (ii) immune activation through release of tumor associated antigens and expression of GM-CSF. It was hypothesized that these effects may co-operate with CRT to increase loco-regional control in stage III/IV SCCHN.

Methods

All 17 patients with stage III/IVA SCCHN with N1-N3 neck disease were recruited. All but one patient had N2/3 disease. Cohorts of four patients received direct injections of up to 4 doses of virus into disease in cervical lymph node(s) using a dose escalation schedule: 10⁶, 10⁶, 10⁶, 10⁶ pfu/mL [cohort 1]; 10⁶, 10⁷, 10⁷ pfu/mL [cohort 2]; and 10⁶, 10⁸, 10⁸ pfu/mL [cohort 3]. An expansion cohort of five additional patients received the same dose schedule as Cohort 3. Viral injections were administered on days 1, 22, 43 and 64. Patients received concomitant full-dose radical CRT comprising 70 Gy in 35 daily fractions on weekdays over seven weeks with cisplatin given on days 1, 21 and 42 at 100 mg/m² body surface area. Resection of involved cervical lymph nodes occurred 6-8 weeks later. In addition to safety, radiological responses, histopathological responses and relapse rates and survival over time were monitored. Levels of anti-HSV antibodies, virus DNA in tumor biopsies, and anti-HSV staining in surgical specimens were also monitored.



Key
█ Cisplatin 100 mg/m² days 1, 22, 43 (intravenous)
█ OncoVEX^{GM-CSF} days 1, 22, 43, 64 (intratumoral into cervical nodal metastasis)
█ Surgery (selective or modified radical neck dissection)

Demographics

Characteristic	OncoVEX ^{GM-CSF} Dose Group				All Patients (N=17)
	Cohort 1 (n=4)	Cohort 2 (n=4)	Cohort 3 (n=5)	Cohort 4 (n=5)	
Age, years					
Mean	59.0	54.5	61.0	47.0	58.0
Range	55-64	50-74	50-64	41-69	41-74
Male	4	3	3	5	15
Female	0	1	2	0	3
ECOG PS					
0	3	3	2	5	13
1	1	1	3	0	5
Primary tumor site					
Oropharynx (palatine tonsil)	1	2	5	3	11
Oropharynx (base of tongue)	1	2	0	1	4
Supraglottis	1	2	0	0	3
Hypopharynx (pyriform fossa)	1	2	0	0	3
T stage					
T0	0	0	0	0	0
T1	0	0	0	0	0
T2	2	5	2	5	14
T3	1	2	1	2	6
T4	1	2	0	0	3
N stage					
N0	0	0	0	0	0
N1	0	0	0	0	0
N2a	0	0	0	1	1
N2b	0	0	0	0	0
N2c	3	7	5	2	17
N3	1	2	0	0	3
Tumor stage					
I	0	0	0	0	0
II	0	0	0	0	0
III	0	0	0	0	0
IVA	3	7	4	1	15
IVB	1	2	0	1	4
IVC	0	0	0	0	0
Previous therapy					
Radiotherapy	0	0	0	0	0
Chemotherapy	0	0	0	0	0

Safety Profile

Chemotherapy was administered on schedule in all 17 patients. Dose reductions were necessary on 7 occasions because of nephro-, neuro- or myelotoxicity. Cisplatin was converted to carboplatin in 1 patient because of ototoxicity. Overall, treatment with OncoVEX^{GM-CSF} was very well tolerated with the only grade 3-4 adverse events noted being those expected from the concomitant therapy with CRT. OncoVEX^{GM-CSF} associated AEs (grade 1-2) were fevers, chills, fatigue/malaise, nausea, and headache, as expected from other studies with the virus. Therefore, with respect to safety, tolerability, and practicality, OncoVEX^{GM-CSF} has been demonstrated to be a well tolerated and easily administered therapy in combination with CRT. The recommended dose schedule for future studies is:

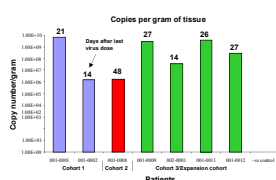
- RT 70 Gy/35 fr/7 weeks
- CDDP 100 mg/m² days 1, 22, 43
- OncoVEX^{GM-CSF} 10⁶, 10⁶, 10⁶, 10⁸ pfu/mL days 1, 22, 43, 64

Adverse Event	OncoVEX ^{GM-CSF} Dose Group				All Patients (N=17)			
	Cohort 1 (n=4)	Cohort 2 (n=4)	Cohort 3 (n=5)	Cohort 4 (n=5)	Grade 3	Grade 4	Grade 3	Grade 4
Any event	3	7	1	2	4	16	1	16
Maximal inflammation	0	0	0	0	2	3	0	3
Dysphagia	3	7	0	0	2	4	0	6
Weight decreased	1	2	0	0	1	2	0	3
Dehydration	0	0	0	0	1	2	0	3
Leucopenia	0	0	0	0	1	2	0	3
Hypotension	1	2	0	0	1	2	0	3
Nausea	1	2	0	0	1	2	0	3
Neutropenia	0	0	0	0	1	2	0	3

Clinical Responses

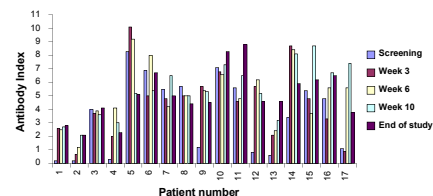
- Seven patients (41%) received fewer than four viral injections because of complete resolution of disease before all cycles were completed, there being no palpable tumor left to inject, and suggestive of a dose related effect. One of these patients elected not to receive surgery as a result.
- 5 patients received 3 injections (1 each from cohort 1 & 2; 3 from cohort 3/expansion)
- 1 patient from cohort 2 received 2 injections
- 1 patient from the expansion cohort received a single injection
- RECIST responses (by radiology)
 - Overall response rate (CR + PR) = 76.4%
 - CR = 17.6%; PR = 58.8%; SD = 23.5%; PD = 0%
- Radiology under-represented the responses observed:
 - 15/16 patients who went for surgery had no evidence of viable tumor in surgical specimens
 - Pathological complete response = 94%
- At a median post-treatment follow-up of 29 months (range 19-40 months)
 - Loco-regional control = 100%
 - 3 patients developed M1 disease (2 at the lowest dose level, 1 of these also developed a 2nd primary head and neck cancer), 2 patients died of intercurrent illness
 - At doses of 10⁷ pfu/ml and above (13 patients) only one patient (7.7%) has relapsed at any site
 - Disease free rate & disease specific survival at ≥10⁷ pfu/ml = 92.3% at 19-34 months follow up

qPCR Suggests Virus Replication



- Biopsies were taken prior to surgery (needle biopsies, arbitrary area of tumor sampled; 4 patients) and at neck dissection (12 patients) at a mean of 27 days after the last virus dose
- HSV DNA was detected at levels higher than the input dose (1x10⁶-4x10⁸ pfu/ml; genome/pfu ratio ~30; distributed throughout the injected tumor)
- This includes in patients in cohort 1 (maximum input 4x10⁶ pfu; 1.2x10⁶ genomes) where up to ~10¹⁰ genomes/g of tumor were detected

Serum Anti-HSV Antibody Levels



- Increased antibody titres were seen in all patients, with a dose-dependent increase between cohort 1 to cohorts 2 and 3

Before treatment

After treatment

Oropharyngeal Primary and Level 2 Nodal Mass

Level 2 Nodal Mass

Level 3 Nodal Mass

Level 3 Nodal Mass

Histology

Extensive tumor necrosis in surgical specimens by H&E staining

Robust staining for HSV in both injected and un-injected nodes demonstrating inter-nodal spread. These results further indicate virus replication. An un-injected node is shown.

Conclusions: The addition of OncoVEX^{GM-CSF} to radical CRT shows promise for the first line treatment of locally advanced stage III/IV SCCHN. Treatment with OncoVEX^{GM-CSF} was easily added to a standard chemoradiation regimen along with each cycle of cisplatin, without significant additional toxicity being observed. Radiological responses, and particularly pathological responses, were impressive, with 94% of patients demonstrated to be tumor free at surgery. Rates of locoregional control at up to 40 months of follow up remains at 100% with no patient experiencing a locoregional relapse so far. Rates of metastatic relapse were also low (17%; all patients), particularly at virus doses ≥10⁷ pfu/ml (7.7%). Disease specific survival at ≥10⁷ pfu/ml is 82.4% at 19-40 months follow up. Overall, the data strongly suggests a benefit of OncoVEX^{GM-CSF} therapy in achieving long term disease control when combined with CRT in patients with SCCHN. As a result, planning for a Phase 3 study is underway.