Phase I/II Trial of Gabapentin Plus Intranasal Ketamine for the Prevention and Treatment of Pain in Patients Undergoing Radiotherapy for Head and Neck Cancer

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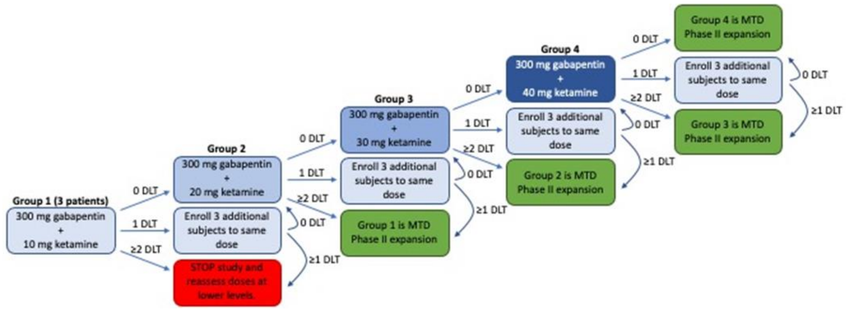
INTRODUCTION

- Pain is common in head and neck cancer (HNC) patients undergoing radiotherapy (RT)[1]
- Gabapentin reduces pain intensity, opioid use, and dysphagia when initiated with RT but dose escalation is limited in some patients due to toxicity[2]
- Novel non-opioid analgesic combinations may address limitations
- Ketamine is a N-methyl-D-aspartate (NMDA) receptor agonist that modulates mood and pain[3]
- Blocking the NMDA receptor may decrease the development/severity of neuropathic pain and decrease or prevent central sensitization[4-6]
- In combination with other analgesics, ketamine may enhance acute and chronic pain control at lower doses and avoid dose-limited toxicities
- We report results from the dose-finding and initial phase II expansion of a study of gabapentin plus intranasal (NAS) ketamine in HNC patients undergoing RT

METHODS

- We conducted a single-institution IRB-approved phase I study to establish the maximum tolerated dose (MTD) of ketamine in combination with gabapentin up to a maximum planned dose (MPD) of 40mg TID
- Primary objective of phase I was to determine the MTD or MPD for NAS ketamine combined with gabapentin.
- A phase II expansion was planned for 20 patients at the MTD/MPD to confirm safety and feasibility, as well as preliminary efficacy.
- Inclusion criteria: Locally advanced, nonmetastatic HNC (T3-4N0M0, T1-4N1-3M0); Planned primary or adjuvant RT or chemoradiation (CRT); ECOG PS 0-2; Age >= 21 years; English speaking
- Exclusion criteria: Currently on gabapentin >300mg TID or ketamine at any dose; Prior non-tolerance of gabapentin or ketamine; Unable to administer ketamine intranasally due to anatomical restriction; History of seizure disorder, schizophrenia, or increased intracranial pressure; Estimated glomerular filtration rate <30 mL/min/1.73 m^2
- Patients were prescribed RT or CRT per standard of care. Gabapentin or ketamine were required to be initiated prior to RT start, with initiation as early as 3 weeks prior to RT. Gabapentin was initiated at 100mg TID for one week and then increased to 300mg TID.
- We used a modified 3+3 dose escalation design using up to 4 different doses of ketamine. Planned ketamine dose levels (DL) were DL1: 10 mg TID, DL2: 20 mg TID, DL3: 30 mg TID and DL 4: 40 mg TID, in combination with gabapentin 300mg TID.
- Patients completed compliance and toxicity diary daily during treatment and completed patient-reported outcome (PRO) surveys and study visits at baseline, weekly during RT treatment, end-of-treatment, and 1-, 2-, and 3-months post-RT.
  - PROs: Vanderbilt Head and Neck Symptom Survey 2.0, Central Sensitivity Index, Head and Neck Pain Inventory, Fibromyalgia Diagnostic Tool, Neurotoxicity Rating Scale
- Dose-limiting toxicity (DLT) was defined as any grade 2 or higher adverse event attributable to ketamine necessitating discontinuation or de-escalation.



RESULTS

- Phase I:
  - 16 patients consented: 2 were ineligible and 3 withdrew due to: decision to forgo treatment; possible metastatic disease; pain medication management per non-VUMC provider. Eleven patients were therefore treated during phase I. No dose limiting toxicities (DLTs) were noted at DL1, DL2, DL3. Two DLTs were reported at DL4: grade 2 dizziness and grade 2 sedation.
  - The MTD was ketamine 30 mg NAS TID.
- Phase II:
  - Thirteen patients are currently enrolled on the phase II trial at the MTD; no DLTs have been reported at the MTD to date.

Table 1. Clinical and Treatment Characteristics of Patients Enrolled on Phase I

Ketamine Dose Level (DL)	Patient #	Age/Sex	Tumor Histology/Primary Site	TNM Stage	RT Dose/Fractions	Concurrent Chemotherapy
DL1 (10mg TID)	1	68 M	squamous cell carcinoma of right palatine tonsil	cT3N2M0	7000cGy/35	carboplatin/paclitaxel
	2	67 M	squamous cell carcinoma of right palatine tonsil	cT2N1M0	6600cGy/30	carboplatin/paclitaxel
	4	45 M	squamous cell carcinoma of left buccal mucosa	pT4aN3b cM0	6000cGy/30	carboplatin/paclitaxel
DL2 (20mg TID)	5	63 F	squamous cell carcinoma of base of tongue	cT3N0M0	6600cGy/30	carboplatin/paclitaxel
	6	62 F	squamous cell carcinoma of left palatine tonsil	pT3 cN1M0	6000cGy/30	carboplatin/paclitaxel
	10	67 F	squamous cell carcinoma of nasopharynx	cT3N0M0	6930cGy/33	carboplatin
DL3 (30mg TID)	12	71 M	squamous cell carcinoma of left base of tongue	cT1N1M0	6996cGy/33	carboplatin/paclitaxel
	13	42 M	squamous cell carcinoma of larynx	cT3N0M0	6996cGy/33	carboplatin
	14	54 M	squamous cell carcinoma of base of tongue	cT1N1M0	7000cGy/35	carboplatin
DL4 (40mg TID)	15	77 F	squamous cell carcinoma of oropharynx	cT4N0M0	6600cGy/30	carboplatin/paclitaxel
	16	78 M	squamous cell carcinoma of left base of tongue	cT2N1M0	7000cGy/25	carboplatin/paclitaxel

Table 2. Grade 2 or Higher Toxicities of Patients Enrolled on Phase I

Ketamine Dose Level (DL)	Patient #	Dose Limiting Toxicities	CTCAE* v 4.0 Grade 2 or Higher Toxicity Experienced
DL1 (10mg TID)	1	No	
	2	No	
	4	No	
DL2 (20mg TID)	5	No	
	6	No	
	10	No	
DL3 (30mg TID)	12	No	
	13	No	
	14	No	
DL4 (40mg TID)	15	Yes	Dizziness requiring discontinuation of ketamine
	16	Yes	Dizziness and sedation requiring discontinuation of ketamine

*CTCAE = Common Terminology Criteria for Adverse Events

CONCLUSIONS

- The MTD of NAS ketamine was 30mg TID combined with gabapentin 300mg.
- The Phase II expansion is ongoing at 30mg TID, with no DLTs reported to date.
- A future randomized clinical trial of gabapentin +/- ketamine is planned.

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ACKNOWLEDGEMENTS: Melanie Copeland, Study Coordinator; Funding: Ingram Industries Pain & Symptom Management Program Endowment; NCATS/NIH grant support for REDCap use (UL1 TR000445)

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