#2263: MULTIMODALITY ASSESSMENT OF ORAL MUCOSITIS IN A PHASE IB TRIAL ON INNOVATIVE NG11-2 DRUG TO REDUCE RADIOTHERAPY-INDUCED MOUTH ULCERATION

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Introduction

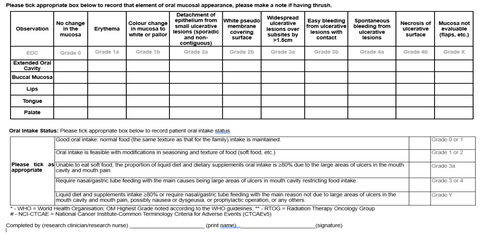
Oral mucositis (OM) is a debilitating side-effect of radiotherapy (RT) and systemic therapy particularly in patients with head and neck cancers (HNC). OM assessment is challenging with several scoring systems and can be highly subjective. Topical application of vasoconstrictors has shown promising effects as prophylactic therapeutics in previous studies (Li NF, 2022). NG11-2, a vasoconstrictor investigational pharmaceutical mouthwash is currently in Phase-Ib dose-escalation study in the UK (EudraCT Number: 2022-002409-99; IRAS Number 1004528). This Phase-Ib study incorporates multimodality (clinical examination, functional evaluation and patient reported outcome measures (PROM)) in OM assessment.

Materials and Methods

Materials: NG11-2 drugs are supplied at four dose strengths: 0.92mg/ml, 1.83mg/ml, 3.66mg/ml and 5.5mg/ml.

Patients: Patients with HNC undergoing RT with/without chemotherapy scheduled to receive a mean radiation dose of no less than 30Gy to the oral cavity according to delineation of Organ-At-Risk Guideline (Brouwer et al 2015), considered to have the high likelihood of developing severe OM, are included in the study.

Methods: The study follows a "2+4" Dose Escalation design (Revathi 2017). The primary endpoint is the occurrence of Dose Limiting Toxicity (DLT) and serious adverse events (SAE). The secondary endpoints include the incidence, duration and the time-to-onset of severe OM defined as ≥ Grade 3 OM in WHO/RTOG/CTCAEv5.0 scales. OM is assessed by using a multimodality assessment worksheet and a PROM questionnaire (samples below).


VasoDynamics Protocol NG11-2 P1b | Oral Mucositis Assessment Scoring Sheet (Version 4.1- Dated 11-Sep-23)

Site number:_____ Patient ID:_____ Please circle: Cycle 1_2 3 4 5 6 7 | Day 1 2 4 5 | Follow-up Day 7 14 28 42

Assessment Date:_____ OM Highest Grade noted: WHO#:_____ RTOG#:_____ NCI-CTCAE#:_____

Please tick appropriate box below to record that element of oral mucosal appearance, please make a note if having thrush.

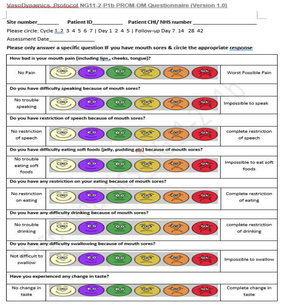
Observation	No change in the mucosa	Erythema	Colour change in mucosa to white or patios	Detachment of epithelium from small ulcerative lesions (sporadic and non-contiguous)	White pseudo membrane covering surface	Widespread ulcerative lesions over subsites by >1.5cm	Easy bleeding from ulcerative lesions with contact	Spontaneous bleeding from ulcerative lesions	Necrosis of ulcerative surface	Mucosa not evaluable (flaps, etc.)
EOC	Grade 0	Grade 1a	Grade 1b	Grade 2a	Grade 2b	Grade 3a	Grade 3b	Grade 4a	Grade 4b	Grade X
Extended Oral Cavity										
Buccal Mucosa										
Lips										
Tongue										
Palate										

Oral Intake Status: Please tick appropriate box below to record patient oral intake status

Please tick as appropriate	Good oral intake: normal food (the same texture as that for the family) intake is maintained.	Grade 0 or 1
	Oral intake is feasible with modifications in seasoning and texture of food (soft food, etc.)	Grade 1 or 2
	Unable to eat soft food, the proportion of liquid diet and dietary supplements oral intake is ≥80% due to the large areas of ulcers in the mouth cavity and mouth pain.	Grade 3a
	Require nasal/gastric tube feeding with the main causes being large areas of ulcers in mouth cavity restricting food intake.	Grade 3 or 4
	Liquid diet and supplements intake ≥80% or require nasal/gastric tube feeding with the main reason not due to large areas of ulcers in the mouth cavity and mouth pain, possibly nausea or dysgeusia, or prophylactic operation, or any others.	Grade Y

* - WHO = World Health Organisation; OM Highest Grade noted according to the WHO guidelines; ** - RTOG = Radiation Therapy Oncology Group
# - NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events (CTCAEv5).

Completed by (research clinician/research nurse) _____ (print name)_____(signature)


VasoDynamics Protocol NG11-2 P1b PROM OM Questionnaire (Version 1.0)

Site number:_____ Patient ID:_____ Patient CHI/ NHS number:_____

Please circle: Cycle 1_2 3 4 5 6 7 | Day 1 2 4 5 | Follow-up Day 7 14 28 42

Assessment Date:_____

Please only answer a specific question IF you have mouth sores & circle the appropriate response.

How bad is your mouth pain (including lips, cheeks, tongue)?		
No Pain	0 1 2 3 4 5 6 7 8 9 10	Worst Possible Pain
Do you have difficulty speaking because of mouth sores?		
No trouble speaking	0 1 2 3 4 5 6 7 8 9 10	Impossible to speak
Do you have restriction of speech because of mouth sores?		
No restriction of speech	0 1 2 3 4 5 6 7 8 9 10	complete restriction of speech
Do you have difficulty eating soft foods (jelly, pudding etc) because of mouth sores?		
No trouble eating soft foods	0 1 2 3 4 5 6 7 8 9 10	Impossible to eat soft foods
Do you have any restriction on your eating because of mouth sores?		
No restriction on eating	0 1 2 3 4 5 6 7 8 9 10	Complete restriction of eating
Do you have any difficulty drinking because of mouth sores?		
No trouble drinking	0 1 2 3 4 5 6 7 8 9 10	complete restriction of drinking
Do you have any difficulty swallowing because of mouth sores?		
Not difficult to swallow	0 1 2 3 4 5 6 7 8 9 10	Impossible to swallow
Have you experienced any change in taste?		
No change in taste	0 1 2 3 4 5 6 7 8 9 10	Complete change in taste

Results

Two patients were enrolled and treated in each of the four escalating dose levels sequentially; all patients completed at least 6 weeks of RT with/without concomitant CT, with daily administration of NG11-2 mouthwash prior to each fraction of RT. All four dose levels were well tolerated, with no DLT or NG11-2 related SAE reported and no evidence of impact on vital signs post NG11-2 treatment. The readouts of secondary end points such as oral mucositis grades at all four dose levels are reported individually (Fig.1). Grade 3 OM was observed in the patients who were treated at 0.92mg/ml, 1.83mg/ml and 3.66mg/ml levels. There has no grade 4 OM occurrence in all patients treated. A preliminary dose-dependent effect of NG11-2 on the reduction of SOM (grade 3 OM) duration has been observed in the dose escalation cohorts (Fig. 2).

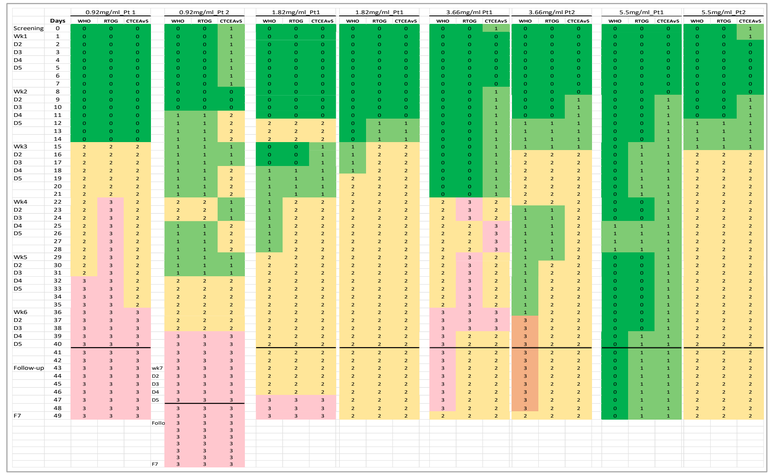


Figure 1. Oral Mucositis (OM) Grade Heatmap up to follow-up day 7. WHO, RTOG and CTCAE v5 OM grades displayed in colour and number codes. Green with number 0 = no change from baseline; Light green with number 1 = OM grade 1, soreness; Yellow with number 2 = OM grade 2, ulcers; Pink with number 3 = OM grade 3, severe OM, liquid diet. Brown = OM grade 3 score only based on liquid diet due to generally poor condition. Black horizontal line indicates the end of radiotherapy. All patients are followed up till 42 days after their radiotherapy (ongoing) .

		0.92mg/ml	1.83mg/ml	3.66mg/ml	5.5mg/ml
Number of SOM (Grade 3 OM)		WHO 2 RTOG 2 CTCAE v5 2	WHO 1 RTOG 1 CTCAE v5 1	WHO 2 RTOG 1 CTCAE v5 1	WHO 0 RTOG 0 CTCAE v5 0 (1 patient still in follow-up)
WHO	Min duration	10	8	4	0
	Max duration	26	8	4	0
RTOG	Min duration	26	22	9	0
	Max duration	33	22	9	0
CTCAE v5	Min duration	12	22	2	0
	Max duration	26	22	2	0

Figure 2. Duration of Severe Oral Mucositis (Grade 3 OM) in patients in dose-escalation phase (date of data extraction: 19th Feb 2024). Two patients were treated in each dose group, the 2nd patient in the last dose level 5.5mg/ml group is still in follow-up at the time of reporting. The duration of SOM is defined as the days between the initial assessment of a WHO (or RTOG or NCI-CTCAE v5) score 3 or above to the last time a WHO (or RTOG or NCI CTCAE v5) score of 3 or above was noted. A trend of a dose-dependent reduction of the SOM duration is observed with the increasing dose levels.

Conclusion

The combination of OM assessment worksheet and PROM questionnaire supports more robust assessment of OM assessment to facilitate precision analysis of drug effects in the clinical trial setting.

This current study provides safety data and preliminary efficacy evidence to support the decision on the Phase II dose level. Subsequent to the dose escalation, enrolment into an 8-patients Expansion Phase is currently ongoing at the highest dose level (5.5mg/ml) to supply additional insight into the characteristics of HNC patient cohorts and the pharmaceutical effect of NG11-2.

Acknowledgments

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References

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3. Li NF, Fahl WE. Reduction of Oral Mucositis Severity Using a Topical Vasoconstrictor in Bone Marrow Transplant Patients. New Frontiers in Medicine and Medical Research. 2022 Vol 10, Chapter 6, p47-55. Print ISBN: 978-93-91882-05-1, eBook ISBN: 978-93-91882-94-5