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EDITORIAL

The Burning Question: Prophylactic Gabapentin for Mucositis-Related Pain in Patients Undergoing Chemoradiation Therapy for Head and Neck Cancer?

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Head and neck cancer (HNC) patients endure a gamut of physical sequelae while undergoing a course of radical chemoradiation therapy (CRT). Of these, mucositis and its related symptoms, including pain, remain particularly troublesome for both the patients and their treating clinicians. Current strategies to manage mucositis-related pain rely heavily on opioids; however, this strategy is frequently inadequate, and consequently, many patients will still experience significant discomfort and pain throughout their treatment. The typical escalation of opioids also introduces a host of additional unwanted challenges, such as nausea and vomiting, sedation, and constipation. These concerns have driven mounting interest in the use of adjunct medications such as gabapentin to increase pain control and possibly reduce the need for high-dose opioids. The Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology recently updated their evidence-based clinical practice guidelines for managing mucositis.[1,2] The recommendations provided for mucositis-related pain relief are focused mainly on systemic opioids and topical morphine, as a paucity of randomized data has prohibited the development of guidelines specifically addressing the role of adjunct analgesics such as gabapentin.[3]

In the article that accompanies this editorial, Cook et al[4] report the results of a randomized, placebo-controlled, double-blind phase 3 study evaluating the role of prophylactic gabapentin in reducing treatment-related oral mucositis symptoms in patients with oropharyngeal cancer treated with definitive CRT. Eligible patients had stage III to IV disease (American Joint Committee on Cancer *Cancer Staging Manual*, seventh edition) and could be either human papillomavirus (HPV) positive (49 of 58 [84%]) or negative. All patients received concurrent platinum-based chemotherapy, including carboplatin (7 of 58 [12%]) or high- (32 of 58 [55%]) or low-dose (19 of 58 [33%]) cisplatin. There were competing cooperative group trials enrolling during this period, which were prioritized, and of the 112 study-eligible patients, 65 consented; 58 patients were included in the per-protocol analysis.

The 2 arms were well balanced across relevant demographic, disease, and treatment variables, including baseline opioid use, disease staging, primary and nodal target volumes, and dosimetric factors (mean pharyngeal constrictor and oral cavity doses). Gabapentin was commenced at 300 mg thrice daily during the first week of treatment and increased to 600 mg thrice daily in week 2 (total daily dose 1800 mg)—a dose that was continued through to the week after treatment, at which point patients were quickly weaned off. The placebo was scheduled in a similar fashion, and compliance was documented at weekly interviews, with 12 of 21 doses in any given week considered protocol compliant. Noncompliant patients in the first 2 weeks of treatment (n = 3) were excluded from the final analysis. All patients were recommended lidocaine oral rinses, and opioids were prescribed at the discretion of individual physicians when self-reported pain scores were in excess of 4 of 10 on a

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numerical scale. The timing and insertion of a feeding tube were individualized and at the discretion of the multidisciplinary team.

This study documented patient-reported outcome measures, opioid use, weight loss, and frequency and duration of feeding tube use. The primary endpoint evaluated the change in the Patient-Reported Oral Mucositis Symptom (PROMS) total score over the entire treatment period (baseline to 6-week post-CRT follow-up). The PROMS scale was developed and validated in the bone marrow transplant setting and includes 10 items assessing mouth pain (single item), the functional impact of mucositis (8 items), and taste change (single item) using a visual analog scale. Secondary outcomes included a prespecified analysis of PROMS item 1 (mouth pain) and a composite score of items 4, 5, 6, and 9; health-related quality of life assessed by the Functional Assessment of Cancer Therapy-Head & Neck (FACT-HN); and a composite score of 4 items on the patient-reported outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) relevant to the study toxicities. Repeated-measures analysis of variance demonstrated no between-arm differences in the primary or secondary PROMS endpoints. Interesting, however, was that throughout the study, the primary endpoint scores numerically favored the placebo arm, differences that at times approached but did not reach statistical significance. Importantly, opioid use was also similar for both arms. Similar quality-of-life outcomes were observed with the exception of a smaller negative change from baseline to follow-up in the functional well-being domain of the FACT-HN in favor of the placebo arm (gabapentin −6.0 vs placebo −1.0; $P = .03$). An increase in the composite PRO-CTCAE score also favored the placebo arm (gabapentin 6.5 vs placebo 1.0, $P = .01$). Keeping in mind that investigators were blinded to arm allocation, feeding-tube placement was more frequent in the gabapentin arm (18 of 29 [62.1%] vs 6 of 29 [20.7%]; $P < .01$); however, the median duration of placement was not statistically different (47.5 vs 39.0 days; $P = .82$). Weight loss from baseline to the last week of treatment was also similar (−11.4% vs −10.7%; $P = .81$). Overall, this study concluded that gabapentin was ineffective in reducing mucositis-related symptoms and suggested that patients may be adversely affected across several clinically relevant measures.

This study provides arguably the strongest data to date in evaluating the role of prophylactic gabapentin in HNC patients undergoing CRT, given its homogeneous inclusion criteria and placebo-controlled, double-blind design. A number of published retrospective[3] and prospective[5-7] studies have also reported their outcomes, with mixed results (Table 1). In placing the current study in context, one needs to consider the variations in study design, inclusion criteria (adjuvant/definitive intent, mixed HNC subsites, utilization of induction chemotherapy), gabapentin dosing (protocol specified and received dosing), concomitant analgesics, and the primary assessment of efficacy. A strength to the Cook et al[4] study is the reporting of radiation doses to the mucosa (pharyngeal constrictors and oral cavity), a surprising omission in the other reported series.

To date, only the planned interim analysis by Smith et al[7] has demonstrated any efficacy in pain reduction with prophylactic gabapentin. In this study, 71 HNC patients undergoing CRT (either definitive or adjuvant) had their pain assessed with the 4-item composite pain subscale of the Vanderbilt Head and Neck Symptom Survey.[8] With the use of a proportional odds model adjusted for time and baseline pain scores, the authors reported that gabapentin resulted in a significant reduction in the composite pain subscale (odds ratio = 0.549; 95% confidence interval, 0.364-0.827; $P = .004$). However, when the analysis was restricted to mucositis-related pain, gabapentin failed to show ongoing efficacy. Furthermore, the authors did not observe any reduction in opioid use, an outcome reported in only 1 of the 4 prospective studies. In that study, Hermann et al[6] reported a reduction in the number of patients requiring opioids when treated with high-dose gabapentin. Conversely, patients in the low-dose gabapentin and methadone arm were reported to have lower total opioid requirements. Drawing definite conclusions from this study is difficult owing to differences in gabapentin dosing and the use of different short- and long-acting opioids in the 2 study arms.

One criticism of the current study may be the protocol-specified dosing of gabapentin (1800 mg daily). Daily gabapentin maintenance doses ranged from 900 mg to 2700 mg across the 4 prospective studies. Patients may not tolerate dosages at the higher end of this range, largely due to somnolence and fatigue, and this may be compounded by cisplatin-induced kidney injuries, given gabapentin is exclusively renally eliminated. Although Smith et al[7] recommended titrating to a maximal daily dose of 2700 mg, most patients were maintained at the lower dose of 900 mg daily, providing support for the use of the dose specified by Cook et al.[4] In addition, >80% of participants in the current study had HPV-positive oropharyngeal cancer, a group shown to experience higher rates of acute and subacute mucositis and more severe mucositis-related pain.[9,10] Although HPV status was balanced between the 2 arms in the current study, it is possible that gabapentin is simply too weak a remedy for this kind of pain.

There are some caveats to this study. The analysis was per protocol rather than intention to treat, and arguably patients who were noncompliant (n = 3) or who experienced acute renal impairment during treatment (n = 1) should not have been excluded from the analysis. The study may also have been slightly underpowered; however, any effect seen in this study was in favor of the placebo arm, and it is very unlikely that a slightly larger study would have yielded a benefit in favor of gabapentin. Although the instrument (PROMS) used for primary assessment of efficacy has not been specifically validated in the studied population, its validity has been tested in patients with oral mucositis in other settings and seems highly likely to be fit for this purpose.

So, where to go from here? Dr Cook and colleagues[4] should be commended for conducting this important study

Table 1 Randomized studies evaluating the role gabapentin in head and neck cancer populations undergoing chemoradiation therapy

Study	No.	Disease site	Treatment received	RT and chemo schedule	Study design	Protocol-specified gabapentin dosing	Received gabapentin dosing	Other analgesic information	Primary endpoint/ pain assessment	Outcome	Opioid use
Current study[4]	58	OPC	All definitive CRT	70 Gy/35 fractions	Randomized, placebo controlled, double blind	Week 1: 300 mg tid Week 2: 600 mg tid through to 1 wk after treatment; then 300 mg tid for 1 d	1 Noncompliant (placebo arm); 3 patients excluded in per-protocol analysis	Opioids at discretion of treating physician (once >4 of 10 pain)	Total PROMS score	No improvement in treatment-related oral mucositis symptoms or pain	No difference
Kataoka et al[5]	22	Mixed: OC 45%; OPC 23%; LC/HPC 27%; NPC 5%	Mixed; Sx + aCRT 45%; NACT 9%	≥60 Gy	Randomized, open label	D1: 300 mg daily; D4: 600 mg daily; D7: 900 mg daily maintained to 4 wk post	2 Patients reduced dose	Analgesic ladder from acetaminophen to incorporation of short- and then long-acting opioids (type not stipulated)	Maximum VAS pain score	No benefit (numerically worse scores in gabapentin arm)	Not reported
Hermann et al[6]	60	Mixed; OC 62%; OPC 25%; LC/HPC 18%; CUP 7%; NPC 7%	All definitive CRT	70 Gy/35 fractions	Randomized, open label	Arm 1: up titrate from D1 evening 300 mg to 900 mg tid over 9 d as tolerated; arm 2: D1: 300 mg; D2 300 mg bid; D3: 300 mg tid and continued; up titrate methadone as long acting	Arm 1: 87%; arm 2: 93% compliant	Arm 1, BT: acetaminophen 325 mg, hydrocodone 7.5 mg qid; long acting: fentanyl transdermal patch (titrated from 25 μg/h); arm 2, BT: oxycodone 5-10 mg Q4h; long acting: methadone 5 mg bid up to 15 mg bid	OMWQ-HN*	No difference in mouth or throat symptoms or pain	Arm 2 had nonsignificant lower MME; more patients in arm 1 did not use any opioids (42% vs 7%)
Smith et al[7,†]	71	Mixed; OPC 55%; LC/HPC 13%; OC 10%; NPC 5%; other 5%	Mixed; Sx + aCRT 23%; NACT 28%	69-70 Gy definitive; 50-60 Gy adjuvant	Randomized, open label	Week 1: 100 mg tid; Week 2: 300 mg tid; Week 3: 600 mg tid; Week 4: 900 mg tid	Most patients were maintained on 300 mg tid	BT and long acting as needed (type not stipulated)	VHNSSv2 pain scale	Reduction in pain (OR = 0.55)[‡]	No difference in breakthrough opioid pain medication

Abbreviations: aCRT = adjuvant CRT; bid = twice daily; BT = breakthrough; CRT = chemoradiation therapy; CUP = carcinoma unknown primary; HPC = hypopharyngeal cancer; LC = laryngeal cancer; MME = morphine milligram equivalent; NACT = neoadjuvant chemotherapy; NPC = nasopharyngeal cancer; OC = oral cavity cancer; OMWQ-HN = oral mucositis weekly questionnaire-head and neck cancer; OPC = oropharyngeal cancer; OR = odds ratio; PROMS = Patient-Reported Oral Mucositis Symptom; Q4h = every 4 hours; qid = 4 times a day; RT = radiation therapy; Sx = surgery; tid = 3 times a day; VAS = visual analog scale; VHNSSv2 = Vanderbilt Head and Neck Symptom Survey version 2.

* Primary endpoint was clinician reported.

† Interim analysis.

‡ suggests that patient on the gabapentin arm would have approximately 55% chance of exceeding a given pain score compared to a patient in the standard therapy arm.

and providing the most compelling evidence to date on the efficacy of prophylactic gabapentin in managing mucositis-related symptoms and pain during HNC-CRT. Although this study comes with several caveats, it is the only placebo-controlled, double-blind study available, thus providing results that are likely to be the least biased. Although larger, well-designed studies would be welcome in the future, there is, at present, little evidence to recommend prophylactic gabapentin during HNC-CRT. Treatment of mucositis-induced pain in HNC patients receiving CRT remains an unmet need, and preclinical and clinical research efforts are required to find novel solutions to this highly demanding symptom.

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