Original Article

Gabapentin for the Treatment of Pain Syndrome Related to Radiation-Induced Mucositis in Patients With Head and Neck Cancer Treated With Concurrent Chemoradiotherapy

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BACKGROUND: This retrospective study evaluated the efficacy of gabapentin for the treatment of pain syndromes related to radiation-induced mucositis in patients with head and neck cancers treated with concurrent chemoradiation. **METHODS:** Data from 42 patients with head and neck malignancies treated with concurrent chemoradiotherapy using an intensity-modulated radiotherapy technique were analyzed. Gabapentin was initiated in the second week of radiotherapy. Opiates were prescribed in addition to gabapentin as clinically indicated to obtain adequate pain control. **RESULTS:** At a median dose of 2700 mg/day of gabapentin, only 33% and 55% of patients required additional low-dose narcotic medications for pain control during the third and fourth week of treatment, respectively, despite exhibiting a grade 2 or higher mucositis in 71% and 86% of the patients, respectively. Furthermore, during the last weeks of treatment, 71% of the patients required additional low-dose opiates for adequate pain control, despite the presence of grade 2 or higher mucositis in 95% and 100% of patients at Weeks 5 and 6, respectively. Only 1 patient had a treatment-related interruption of >3 days during chemoradiotherapy. **CONCLUSIONS:** Gabapentin appears to be promising in reducing the need for high total doses of opioids and avoiding unplanned treatment interruptions for patients with head and neck malignancies treated with concurrent chemoradiotherapy and should be further evaluated prospectively in controlled clinical trials. ***Cancer*** **2010;116:4206–13.** © *2010 American Cancer Society.*

KEYWORDS: gabapentin, radiation-induced mucositis, chemoradiation, head and neck malignancies, pain control.

Patients undergoing radiotherapy for the head and neck malignancies develop painful mucositis, which often result in decreased oral intake, weight loss, decreased quality of life, and unforeseen treatment interruptions.[1,2] Concurrent chemotherapy with radiotherapy is associated with a significantly increased frequency, severity, and duration of oral mucositis.[1] The pathogenesis of radiation-induced mucositis is multifactorial and appears to be more complex than direct damage to the epithelium.[3,4] Recent studies have demonstrated that patients with head and neck cancer experience nociceptive and neuropathic pain during their radiotherapy course, suggesting the need to treat both types of pain.[5]

Although opioids are the mainstay for the treatment of cancer pain management, their use is limited not only by common side effects such as depression, sedation, nausea, vomiting, constipation, pruritus, and respiratory depression, but also by the fact that neuropathic pain responds poorly to narcotics and requires escalating doses.[6-8]

Gabapentin has been effectively used to treat multiple neuropathic pain syndromes such as chronic pain, diabetic neuropathy, postherpetic neuralgia, trigeminal neuralgia, and postoperative pain, but to the best of our knowledge only limited data exist regarding its efficacy for other pain syndromes.[9-14] Recent studies have demonstrated the efficacy of

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Table 1. Patient and Treatment Characteristics

Characteristic	No. of Cases (%)	
Sex		
Male	30	(71)
Female	12	(29)
Type of cancer		
Oropharyngeal squamous cell carcinoma	16	(38)
Oral cavity squamous cell carcinoma	7	(16.5)
Laryngeal and hypopharyngeal squamous cell carcinoma	7	(16.5)
Paranasal sinuses carcinoma	5	(12)
Sinonasal undifferentiated carcinoma	5	(12)
Nasopharyngeal squamous cell carcinoma	2	(5)
Induction chemotherapy		
Yes	7	(17)
No	35	(83)
Concurrent chemoradiotherapy		
Definitive	24	(57)
Postoperative	18	(43)
Surgery prior to radiotherapy		
Yes	18	(43)
No	24	(57)

gabapentin in improving the pain control in patients with neuropathic cancer pain who already have been treated with opiates.[15]

We previously demonstrated that gabapentin at median doses of 2700 mg/day appeared promising in reducing the need for narcotic pain medication for patients with head and neck malignancies treated with intensity-modulated radiotherapy (IMRT) without concurrent chemotherapy.[14] In the current retrospective review, we evaluated the efficacy of gabapentin for the treatment of pain syndrome related to radiation-induced mucositis for patients with head and neck tumors treated with concurrent chemoradiotherapy.

MATERIALS AND METHODS

Patient Selection

The information for this retrospective analysis was collected from the medical records of patients treated in the Department of Radiation Oncology at the University of Pennsylvania. Institutional Review Board approval was granted for the conduct of this study. The study cohort was represented by 42 patients diagnosed with head and neck cancer and treated with concurrent chemoradiation between December 2003 and November 2006. Patient characteristics are shown in Table 1. Patients already taking narcotic pain medications before chemoradiation treatments were excluded from this retrospective review.

Surgery

Eighteen (43%) patients underwent surgical resection of the primary tumor and were treated postoperatively with concurrent chemoradiation. Unilateral or bilateral selective neck dissections were performed in 14 (33%) of the patients before chemoradiotherapy.

Radiotherapy

Radiation was delivered using IMRT that incorporated a simultaneous in-field boost technique. Radiotherapy was delivered to the primary tumor site and bilateral cervical lymph nodes in all patients.

For the patients who were biopsied only and undergoing definitive chemoradiotherapy, median doses of 57.6 Grays (Gy) (range, 50-61.25 Gy), 64 Gy (range, 54-70 Gy), and 70.4 Gy (range, 66-75.6 Gy) were delivered to the low-risk planning target volume (LRPTV), high-risk planning target volume (HRPTV), and macroscopic tumor volume, respectively. The median dose per fraction prescribed was 1.8 Gy (range, 1.75-2 Gy) to the LRPTV, 2.1 Gy (range, 2.0-2.1 Gy) to the HRPTV, and 2.2 Gy (range, 2.0-2.2 Gy) to the macroscopic tumor volume. A median of 32 (range, 29-35) treatment fractions were delivered.

For the patients treated with postoperative chemoradiotherapy, median doses of 54 Gy (range, 54-61.25 Gy), 60 Gy (range, 60-63 Gy), and 66 Gy (range, 60-66 Gy) were delivered to the LRPTV, HRPTV, and boost target

volume, respectively. The dose per fraction prescribed was 1.8 Gy to the LRPTV, 2 Gy or 2.1 Gy to the HRPTV, and 2.1 Gy or 2.2 Gy to the boost target volume. Thirty treatment fractions were delivered to all patients receiving postoperative concurrent chemoradiation.

All patients were treated once daily to all target volumes, 5 fractions per week, with 6-megavolt photons using a simultaneous boost technique. The median number of beams used for the IMRT treatment delivery was 7 beams (range, 6-14 beams).

Chemotherapy

All patients in this cohort received systemic therapy during their radiotherapy. Twenty-one patients (50%) received platinum-based chemotherapeutic regimens delivered every 3 weeks: cisplatin at a dose of 100 mg/m^2 every 3 weeks in 19 patients, cisplatin at a dose of 75 mg/m^2 combined with etoposide at a dose of 100 mg/m^2 on Days 1 to 3 every 3 weeks in 1 patient, and cisplatin at a dose of 75 mg/m^2 every 3 weeks combined with weekly cetuximab at a dose of 400 mg/m^2 on Day 1 followed by weekly C225 at a dose of 250 mg/m^2 thereafter in 1 patient. Eighteen patients (43%) received weekly systemic therapy, including weekly carboplatin (area under the curve, 2) and weekly paclitaxel at a dose of 30 mg/m^2 in 17 patients and weekly C225 at a dose of 400 mg/m^2 on Day 1 followed by weekly C225 at a dose of 250 mg/m^2 thereafter for 1 patient. The concurrent chemotherapeutic regimen was unknown in 3 patients (7%). Seven patients (17%) in this group received induction chemotherapy before concomitant chemoradiation.

Pain Medication

Gabapentin was initiated at a dose of 600 mg taken at bedtime in the second week of chemoradiation. The dose was gradually increased over 1 week to 900 mg taken 3 times per day for a total daily dose of 2700 mg/day. The dosage of gabapentin used in this study was in accordance with the published literature demonstrating that, at doses of 1800 to 3600 mg/day, gabapentin was effective in the treatment of adults with neuropathic pain.[16] Opiate pain medication (oxycodone) was prescribed as needed in addition to gabapentin in response to the patient's subjective pain scores. For patients who did not tolerate oral oxycodone, additional parenteral fentanyl or other opioids were prescribed and an equianalgesic dose ratio between different opioids was used to convert their specific dose to an oxycodone-equivalent dose.[17]

Feeding Tube Placement

Thirty-nine (93%) patients underwent a percutaneous endoscopic gastrostomy (PEG) tube placement to maintain adequate nutrition for the duration of chemoradiotherapy and the weeks following. This practice reflects our institutional policy recommending prophylactic PEG tube placements for all patients receiving concurrent chemoradiotherapy. All but 1 patient had the feeding tube placed before the initiation of concurrent chemoradiation. One patient underwent placement of the feeding tube in the last few weeks of treatment due to weight loss and need for frequent intravenous hydration. Three (7%) patients refused feeding tube placement for the entire duration of treatment.

Toxicity Assessment

Radiation-induced mucositis was assessed for each patient on a weekly basis using Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. Grade 0 mucositis was defined as no oral cavity or oropharyngeal mucosal changes. Grade 1 mucositis was defined as erythema of the mucosa. Grade 2 mucositis was defined as a patchy pseudomembranous reaction (patches measuring $\leq$1.5 cm in dimension and noncontiguous). Grade 3 mucositis was defined as confluent pseudomembranous reaction (contiguous patches measuring $>$1.5 cm in dimension). Grade 4 mucositis was defined as necrosis or deep ulceration.

Dysphagia due to radiation was assessed for each patient on a weekly basis using CTCAE. Grade 0 dysphagia was defined as no swallowing difficulty. Grade 1 dysphagia was defined as difficulty swallowing but still able to eat a regular diet. Grade 2 dysphagia was defined as difficulty swallowing requiring predominantly a pureed, soft, or liquid diet. Grade 3 dysphagia was defined as difficulty swallowing requiring feeding tube, intravenous hydration, or hyperalimentation. Grade 4 dysphagia was defined as complete obstruction (not able to swallow saliva), ulceration with bleeding not induced by minor trauma or abrasion, or perforation.

Patients were monitored on a weekly basis and examined for other treatment-related toxicity, such as pain control, and adjustments to their pain medication schedule were made accordingly. The technique for evaluation of mucositis was primarily by means of intraoral examination. However, for the patients diagnosed with laryngeal cancers and for the patients diagnosed with nonlaryngeal tumors who developed severe treatment-related toxicity, nasopharyngolaryngoscopy was performed as needed during the

duration of chemoradiotherapy and regularly the following weeks after the end of the treatment.

Side effects of gabapentin and additional pain medication were recorded on a weekly basis.

Statistical Analysis

Subgroup differences in grade of mucositis at Week 1 through Week 6, dichotomized between grades 0 and 2 versus grade ≥3, were tested using the Fisher exact test or Pearson chi-square test. Subgroups analyzed included patients with laryngeal (7 patients) versus nonlaryngeal (35 patients) primary site of disease, as well as patients who received cisplatin-based chemotherapeutic regimens delivered every 3 weeks (21 patients) versus patients who received weekly chemotherapeutic regimens (18 patients).

Early opioid use during the second week of radiotherapy was reported. Subgroup differences in early opioid use were tested using the Pearson chi-square test for patients who underwent surgery before radiotherapy (18 patients) versus patients who did not undergo surgery (24 patients) before their radiotherapy.

All *P* values for proportional differences in the subgroups analyzed were 2-sided and considered significant if <.05. Analysis was performed with JMP for Windows statistical software, version 8.0.1 (JMP Macintosh product for Microsoft Windows statistical software).

RESULTS

The median age of the patients in this cohort was 53 years (range, 30-78 years). The median duration of follow-up was 6 months (range, 1-33 months).

Mucositis Due to Radiation

All patients in the current study developed mucositis necessitating narcotic pain medication. Grades 1 and 2 mucositis occurred during the first 2 weeks of chemoradiotherapy in 37 (88%) patients, with half of these patients experiencing grade 2 mucositis during the second week of treatment. No grade 3 mucositis was reported during the first 2 weeks. By the third and fourth week of treatment, grade 2 or higher mucositis was present in 71% and 86% of the patients, respectively. The incidence of grade 3 mucositis increased to 17% during the third week of radiation and to 45% of patients by the fourth week of chemoradiation. Approximately 95% of the patients in the current study developed grade 2 or 3 mucositis by the fifth week of treatment, with 60% of the patients presenting with grade 3 mucositis. All patients in this cohort experienced grade 2 or higher mucositis by the sixth week of treatment, with 81% of the patients exhibiting grade 3 mucositis. Twenty-two patients undergoing 7 weeks of treatment experienced grade 2 or 3 mucositis, with 77% demonstrating grade 3 mucositis. No grade 4 mucositis was reported for this study group. These results are illustrated in Figure 1.

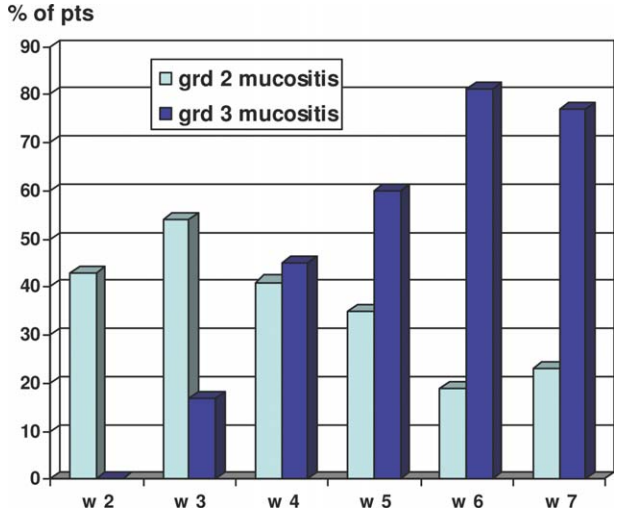

Figure 1. Grade (grd) 2 and grade 3 radiation-induced mucositis during chemoradiotherapy is shown in weeks (w). No grade 4 mucositis was reported. pts indicates patients.

Severity of Radiation-Induced Mucositis (≥ Grade 3 Mucositis as Opposed to Grades 0 to 2) for Patients With Laryngeal Versus Nonlaryngeal Sites of Disease

No grade 3 or higher mucositis was reported during the first 2 weeks of radiotherapy. There was no statistically significant difference with regard to severity of mucositis (≥ grade 3 mucositis vs grades 0-2) between patients with laryngeal sites of disease versus patients with nonlaryngeal tumors at Week 3 of radiotherapy (Fisher *P* value, .326). The difference in severity of mucositis (≥ grade 3 mucositis vs grades 0-2) between the groups of patients with laryngeal versus nonlaryngeal primary sites of disease at Week 4 of radiotherapy was statistically significant (Fisher *P* value, .011), with a larger proportion of grade 3 or higher mucositis reported for patients with laryngeal primary sites of disease. However, the difference in severity of mucositis (≥ grade 3 mucositis vs grades 0-2) between the groups of patients with laryngeal versus nonlaryngeal primary site of disease returned to a statistically nonsignificant level during the last weeks of radiotherapy (Fisher *P* value, .099 for Week 5 and Fisher *P* value, 1.0 for Week 6, respectively).

Severity of Radiation-Induced Mucositis (≥ Grade 3 Mucositis Versus Grades 0-2) for Patients Who Received Concurrent Cisplatin-Based Chemotherapeutic Regimens Delivered Every 3 Weeks Versus Patients Who Received Weekly Chemotherapeutic Regimens

No grade 3 or higher mucositis was reported during the first 2 weeks of radiotherapy. There was no statistically significant difference in severity of mucositis (≥ grade 3 mucositis vs grades 0-2) between patients who received cisplatin-based chemotherapeutic regimens delivered every 3 weeks versus patients who received weekly chemotherapeutic regimens at Weeks 3 and 4 of radiotherapy (Pearson *P* value, .138 for Week 3 and Pearson *P* value, .083 for Week 4 of radiotherapy, respectively). However, the difference in severity of mucositis (≥ grade 3 mucositis vs grades 0-2) between patients who received cisplatin-based chemotherapeutic regimens delivered every 3 weeks versus patients treated with weekly concurrent chemotherapeutic regimens achieved statistical significance at Week 5 and 6 of radiotherapy, with a larger proportion of patients who received weekly chemotherapeutic regimens found to develop severe mucositis (Pearson *P* value, .054 for Week 4 and Pearson *P* value, .014 for Week 6, respectively).

Dysphagia Related to Radiotherapy

Forty (95%) patients in this study developed grade 1, 2, or 3 dysphagia at some point during their treatment course. Only 2 (5%) patients reported difficulty with swallowing (grade 1 dysphagia) at the end of the first week of treatment. However, 16 (38%) patients experienced grade 1 or 2 dysphagia by Week 2, and 22 (52%) patients by Week 3. By Week 4, 32 (76%) patients experienced swallowing difficulty, 15 of whom (36%) reported grade 2 or 3 dysphagia. Swallowing difficulty was reported in 40 (95%) patients by Weeks 5 and 6, with 20 (48%) patients reporting grade 2 or 3 dysphagia. Dysphagia remained stable during the seventh week of treatment. No grade 4 dysphagia was reported for this study cohort.

Pain Management

No patient required pain medication during the first week of treatment in this study. Three (7%) patients in this cohort refused the use of gabapentin for their pain management and were treated with only opiates at some point during their course of chemoradiotherapy; the opioid doses were gradually increased during the course of chemoradiotherapy for a better pain control. During the last weeks of treatment, 2 of these patients received 90 mg/day of oxycodone-equivalent and 1 patient was treated with 180 mg/day of oxycodone-equivalent. One patient was treated with opioids only at a dose of 90 mg/day of oxycodone-equivalent for the majority of his course of chemoradiotherapy, and agreed with to the addition of gabapentin at a dose of 2700 mg/day for better pain control only during the last 2 weeks of radiotherapy. Gabapentin was initiated in the second week of radiotherapy in 38 (90.5%) patients, with only 5 (12%) patients using an additional median dose of 10 mg/day of oxycodone-equivalent (range, 5-65 mg/day) for satisfactory pain control. By Week 3, 38 (90.5%) patients were prescribed a median dose of 2700 mg/day of gabapentin, with only 14 (33%) patients requiring an additional median dose of 10 mg/day of oxycodone-equivalent (range, 5-90 mg/day) for adequate pain relief, despite the presence of grade 2 or higher mucositis in 71% of these patients. During the fourth week of chemoradiation, 38 (90.5%) patients continued on a median dose of 2700 mg/day of gabapentin; only 23 (55%) patients required an additional median dose of 30 mg/day of oxycodone-equivalent (range, 10-150 mg/day) for adequate pain control, despite the presence of grade 2 or higher mucositis in 86% of these patients. Finally, during the last weeks of treatment, 38 (90.5%) patients were continued on a median dose of 2700 mg/day of gabapentin, but 30 (71%) patients required an additional median dose of 60 mg/day of oxycodone-equivalent (range, 10-180 mg/day) for adequate pain control, despite the presence of grade 2 or higher mucositis in 95% to 100% of patients. Pain medication was continued through the last week of treatment, and for several weeks after the end of chemoradiation. During follow-up after completion of chemoradiotherapy, patients were gradually weaned off of narcotic pain medication first and then off of gabapentin.

In summary, no pain medication was required during the first week of radiotherapy and opioid use during the second week of radiotherapy was reported at low doses. There was no statistically significant difference in the early use of opioids between patients who underwent surgery before radiotherapy versus patients who did not undergo surgery before radiotherapy (Pearson *P* value, .27).

Gabapentin-Related Toxicity

Gabapentin was well-tolerated by the majority of patients. Only 2 (5%) patients experienced mild side effects, comprised of dizziness. These side effects were managed by reducing the dose from 2700 mg/day to 1800 mg/day.

Radiation Treatment Interruptions

Only 1 (2.4%) patient had interruptions of treatment of >3 days related to chemoradiotherapy toxicity (hospitalization for aspiration pneumonia).

DISCUSSION

Radiation-induced oral mucositis is a common treatment-limiting toxicity of chemoradiotherapy for head and neck cancers. Oral mucositis presents initially as erythema of the oral mucosa, which frequently progresses to erosion and ulceration, causing severe pain.[3,4] Radiation-induced oral mucositis is potentially influenced by multiple factors, including primary tumor site, chemotherapeutic regimen delivered concurrently with radiotherapy, size of radiation fields, and total doses of radiation.[3] The difference in severity of mucositis (≥ grade 3 mucositis vs grades 0-2) between the groups of patients with laryngeal versus nonlaryngeal primary sites of disease at Week 4 of radiotherapy was statistically significant, with a larger proportion of grade 3 or higher mucositis reported for patients with laryngeal primary sites of disease; however, the difference in severity of mucositis (≥ grade 3 mucositis vs grades 0-2) between the groups of patients with laryngeal versus nonlaryngeal primary sites of disease returned to a statistically nonsignificant level during the last weeks of radiotherapy. Nonetheless, we acknowledge the limitations of the retrospective nature of the current study and the small sample analyzed. Moreover, the difference in severity of mucositis (≥ grade 3 mucositis vs grades 0-2) between patients who received cisplatin-based chemotherapeutic regimens delivered every 3 weeks versus patients who received weekly chemotherapeutic regimens was statistically significantly different at Weeks 5 and 6 of radiotherapy, with a larger proportion of grade 3 or higher mucositis reported in the group of patients who received weekly chemotherapeutic regimens. The majority of patients receiving weekly systemic therapy in this cohort were treated with weekly carboplatin and paclitaxel. It is likely that a higher rate of grade 3 or higher mucositis reported in this group of patients was related to the addition of weekly paclitaxel concurrently with irradiation. Hoffmann et al demonstrated that the dose-limiting toxicity for weekly paclitaxel delivered concurrently with radiotherapy was oral mucositis; hematologic and other nonhematologic toxicities were mild.[18]

Recent studies have demonstrated that patients with head and neck cancer experience nociceptive and neuropathic pain during their radiotherapy course, suggesting the need to treat both types of pain.[5] Moreover, neuropathic cancer pain appears to be less responsive to opioids and represents a major problem in cancer pain management.[19]

Gabapentin, initially developed as an antiepileptic drug, was later discovered to be effective in the treatment of neuropathic pain having antinociceptive and antihyperalgesic properties.[9] To the best of our knowledge, the mechanism of action of gabapentin for pain control is unclear, but the most accepted hypotheses support a reduced neurotransmitter release and attenuation of postsynaptic excitability in the spinal cord, through inhibition of calcium currents by means of the high voltage-dependent calcium ion channels.[20,21]

Opiates and gabapentin are believed to interact favorably through a simultaneous decrease in hyperexcitation and increased inhibition of nociception.[19] Whether these interactions are synergistic or merely additive remains to be fully elucidated. Preclinical studies demonstrated that the combination of gabapentin and opiates results in a synergistic effect.[22] An enhanced analgesic effect of morphine, resulting from the additional administration of gabapentin, was demonstrated in a recent clinical study in healthy volunteers.[23] Furthermore, this combination was found to be better in relieving neuropathic pain than escalating doses of opioid alone in cancer patients or patients with painful diabetic neuropathy or postherpetic neuralgia.[19,24] The combination of gabapentin and morphine also had a beneficial effect on pain-related interference with daily activity, mood, sleep, and quality of life.[16,24] This combination of gabapentin and opioids may represent a potential first-line regimen for the management of pain in cancer patients.[19] In the current study, gabapentin, at a median dose of 2700 mg/day, appeared to reduce the need for high total doses of narcotic pain medication for satisfactory pain control in patients with head and neck malignancies treated with concurrent chemoradiation. The findings of the current study suggest an adequate pain relief with the use of gabapentin and low-dose opioids, thereby reducing the risk of adverse side effects traditionally associated with narcotics in this group of cancer patients.

In addition to its symptomatic impact, oral mucositis increases the likelihood of unplanned treatment interruptions or delays in chemoradiotherapy.[3] The negative effect on survival and locoregional control of unplanned radiotherapy breaks and prolongation of the duration of treatment time for head and neck cancer patients has been well documented in multiple studies.[1,2] Only 1 patient in

the current study had an interruption of >3 days during the treatment, related to chemoradiotherapy toxicity. The findings of the current study have significant implications in achieving better pain relief and allowing patients to continue their radiotherapy without unplanned treatment interruptions.

Furthermore, pain management using gabapentin is associated with good drug tolerability, lack of serious toxicity, and ease of use. Gabapentin is not significantly metabolized in the human body, is entirely excreted by the glomerular filtration apparatus, is not protein-bound, and has no significant drug interactions.[23,24] Clinically, gabapentin has been shown to be safe and well tolerated without significant acute or chronic toxicity. In addition, unlike narcotic medications that potentially have addictive and tolerance properties in certain patient populations, to our knowledge dependence on gabapentin has not been reported to date.[8,12,22] The current study findings are in accord with the previously mentioned reports indicating that gabapentin is well-tolerated by the majority of patients. Only a few individuals experienced mild side effects, comprised mainly of dizziness, which was readily managed by reducing the dose of the drug.

Conclusions

The results of the current study support the use of gabapentin as both an effective and well-tolerated treatment for pain related to radiation-induced mucositis in patients with head and neck malignancies who are treated with concurrent chemoradiation. Gabapentin appears promising in reducing the need for high total doses of opioids and avoiding unplanned treatment interruptions for patients with head and neck malignancies treated with concurrent chemoradiotherapy. Given the potential benefits of gabapentin in combination with opioids for the treatment of pain syndromes related to radiation-induced mucositis, randomized clinical trials are needed to establish the role of this analgesic combination in this group of cancer patients.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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