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The novel role of gabapentin in managing mucositis pain in patients undergoing radiation therapy to the head and neck

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The annual incidence of cancers of the head and neck worldwide is reported as approximately 550,000 cases with an estimated 300,000 deaths annually. In the United States, there is an estimated 45,780 new cases of cancer of the oral cavity and pharynx in 2015 (ACS, 2015). According to the National Cancer Institute (2015), the vast majority (90%) of these cancers arise in the flat squamous cells that line the respiratory and digestive tracts.

Cancers of the head and neck include several site-specific anatomic areas. These areas include the oral cavity, pharynx (including nasopharynx, oropharynx and hypopharynx), larynx, nasal cavity, paranasal sinuses, and salivary glands. (See Figure 1)

Primary management of head and neck cancers may include surgery, radiation, chemotherapy, or a combination. Treatment plans are based on several factors including the stage of the cancer at diagnosis, location of the tumor, and the general health status and or comorbidities of the patient. Radiation therapy (RT) alone or in combination with chemotherapy or targeted therapies has become accepted standard care for locally advanced head and neck cancers (Takes, et al., 2010; Pignon, J. et al., 2007). Chemotherapy and targeted therapies (cetuximab) act as radiosensitizers to radiosensitize tumors and achieve increased cell kill and ideally improve local tumor control (Takes et al., 2010; Lambert, et al., 2010). Patients with locally advanced head and neck cancer treated with chemotherapy and RT were found to have an absolute survival benefit of 7% at five years when compared to patients who received RT alone (Pignon, et al, 2007). The benefits of this nonsurgical approach include avoiding potentially, disfiguring surgeries and maintaining the patient's ability to speak and swallow.(Takes, et al., 2010). However, concurrent treatment with chemotherapy and RT increases the incidence and severity of oral mucositis (OM) to as much as 100% (Eilers, et al., 2014). Oral mucositis in head and neck cancer patients undergoing RT with or without chemotherapy has been reported as the most distressing symptom in their treatment course (Eilers and Million, 2011). High grade OM (grade 3 -4) is associated with significant patient morbidity including pain, inability to chew, swallow, maintain caloric intake, unplanned hospitalizations and an overall worsening quality of life (Trotti, et al., 2003; Eilers, et al., 2014).

With the breach in the oral mucosal membrane, secondary infections may occur resulting in potentially life threatening systemic infections and hospitalizations (Eilers, et al., 2014). Patients who develop severe OM from combined RT and chemotherapy for head and neck cancer are reported to incur 52% higher costs during their treatment when compared to patients who do not develop high grade OM (Mason, H, et al., 2013). This finding illustrates the overall financial impact and potential burden of OM on both the individual and community.

Unplanned treatment breaks in this head and neck cancer population is associated with a reduction in local and regional disease control. The reduction in locoregional disease control is attributable to the biologic basis of radiation and the propensity of malignant tumors to accelerate the repopulation process and lead to development of resistant clones causing further compromising disease control during radiation treatment interruptions (Russo, 2008; Eilers, et al., 2014; Mallick, et. al., 2015).

This paper will describe the presentation, pathophysiology, grading of OM in patients undergoing RT to the head and neck region, and the types of pain these patients experience. The novel role that gabapentin may have as a co analgesic to enhance pain management and possibly prevent escalating doses of opioids is included and the nursing implications of treating OM in patients with head and neck cancers receiving RT.

Mucositis overall is one of the most common complication in patients undergoing cancer treatment (Sonis 2004; Silverman, 2007). The term “mucositis” refers to inflammation along the epithelial cells lining the gastrointestinal tract from the mouth to the rectum. OM is an inflammation of the mucous membranes along the oral cavity including the gingiva, buccal mucosa, tongue and lips. (Bar Ad, V. et al, 2010). OM affects between 80% - 100% of patient undergoing RT to the head and neck (Sonis 2004). It is often a starting point for a cascade of complications that leads to pain, infection, decreased nutritional intake, diminished quality of life, and unplanned treatment breaks, potentially leading to decrease locoregional disease control and patient survival (Mallick, et al., 2015; Trotti, et al., 2003).

The presentation and course of RT induced OM follows a clinically predictable course and is typically given in daily doses referred to as fractions. A common course of RT for treatment of head and neck cancer is approximately 200 cGy given daily five day per week, for an average of five to seven weeks (Sonis, 2012; Kumar, 2009). Oral mucositis is commonly clinically evident by the third week of RT, or after approximately 25-30 Gy has been delivered. It may develop earlier when concomitant chemotherapy or other radiosensitizing medications such as mTor inhibitors or protease inhibitors are being given or if an altered fractionation schedule is used (Russo, G. et. al., 2008). Symptoms may persist for over 4 weeks after treatment is complete. (Sonis, 2012). Early stage OM often presents as erythema of the oral cavity and is commonly described by patients as burning or tingling. The lesions can become confluent and friable, bacterial and fungal colonization and overgrowth can worsen pain leading to systemic infections requiring treatment breaks, hospitalizations for supportive care, and sepsis (Sonis, 2012).

Pathophysiology

The pathophysiology of OM had historically been described as a linear “outside in” process beginning with damage of the superficial epithelial layer of the oral mucosa. However, over the past decade, research has supported a more complex process. Sonis (2004) has postulated a model that describes the dynamic and complex process of OM where the process actually begins in the submucosal endothelium and connective tissue. This deeper damage results in a cascade of biologic pathways that ultimately result in damage to the oral epithelium, ulceration, and potential for microorganisms to enter the bloodstream and lead to systemic infections.

The five stages include initiation, primary damage response, signal amplification, ulceration, and healing. These stages occur in a cyclical fashion throughout the treatment process. Figure 2 describes each phase.

Grading

Consistent and uniform reporting of OM is important in order to compare outcomes of prevention and therapeutic interventions. The use of multiple grading scales made head to head comparison of trials unreliable. There are a variety of grading systems used worldwide to grade the severity of mucositis include Radiation Therapy Oncology Group (RTOG), the World Health Organization (WHO) and United States National Cancer Institute (US NCI). In 1998 the United States National Cancer Institute (US NCI) developed criteria to describe a variety of toxicities including oral mucositis. The use of the *Common Terminology Criteria for Adverse Events* (CTCAE) provides a standardized grading system used to describe and document OM. See Table 1. The use of a uniform standardized system allows comparisons of multiple studies and can assist in comparing studies and drug trials (Trotti, et al, 2003). The most updated version, CTCAE 4.0 issued on May 29, 2009 (Liu, Yu-Jie, et al; 2012).

There is compelling evidence that oral hygiene and standard oral care protocols are effective in decreasing the severity and delaying onset of OM (Tekinsoy Kartin, P., et al., 2014). Professional organizations including Oncology Nursing Society (ONS), Multinational Association of Supportive Care (MASCC), and the International Society for Oral Oncology recommend that patients receive instruction on oral hygiene using a soft bristle toothbrush, flossing, bland rinses including sodium bicarbonate and saline (Kumar, 2009). Regular oral assessment before, during, and for several weeks following RT is generally recommended. Symptom management including pain control remains a pivotal part of care as no gold standard evidence exists to reliably prevent the development of OM in this population, supportive management is key (Eilers, et al., 2014).

Pain

Pain is a common and often undertreated symptom in the cancer patient and is a nursing sensitive outcome. A nursing sensitive outcome is within the scope of nursing practice and can be greatly impacted specifically by nursing interventions (Aiello-Laws, L, et al., 2009). Pain is reported in up to 85% of patients with head and neck cancer on presentation and may

be the first symptom of head and neck cancer in 20-50% of patients. Pain in the head and neck region is thought to be multifactorial.

Infiltration by the tumor into adjacent tissue and nerves can cause pain. Surgery, chemotherapy or RT can cause tissue and neural destruction. (Epstein, JB. 2009). There has been recent evidence in the literature, that patients with head and neck cancer experience a combination of nociceptive and neuropathic pain (Epstein, JB. 2009; Bar Ad, V.B, et al, 2010).

Nociceptive pain occurs when there is somatic or visceral tissue injury resulting in stimulation of the nociceptive receptors in skin, connective tissue, viscera or muscle. The tissue damage can be a result of thermal, chemical, or mechanical injury. This type of pain is typically described as dull, tender, or throbbing. Mild to moderate nociceptive pain may respond to nonsteroidal anti-inflammatory drugs (NSAIDs) with opioids being recommended for moderate to severe cancer related pain (Vardy, 2014; Dy, 2010; Aiello-Law, et.al., 2009).

Neuropathic pain is estimated to be as high as 40% in the general oncology population (Jordan, et al., 2013) and results from damage to either the central or peripheral nervous system. This can be from the direct result of tumor invasion such as with leptomeningeal disease, nerve plexus invasion, or epidural metastases. Neuropathic pain is often described as aching or burning and is usually poorly relieved with opioids. There is evidence to support that a significant percentage of patients with head and neck cancer experience neuropathic pain. (Dy, 2010; Aiello-Laws, 2009).

Literature on the specific recommendation of use of systemic analgesics to treat pain from OM is sparse (Stenstrom, and Larsson, 2011). The mainstay of OM pain management has been opioid therapy often leaving the patient open for additional life altering side effects including depression, sedation, nausea, vomiting, constipation, pruritus, and respiratory depression. Opioid pain medications have been found to be less effective in neuropathic pain even with dose escalations (Bar Ad, V et al., 2010). Co analgesics can play an important role in improving pain management along side of narcotic pain medications (Aiello-Laws, L et al, 2009). They can assist in preventing dose escalations of opioids and address the often untreated neuropathic components of certain pain syndromes (Bar Ad, V.B., 2010). Co analgesics (also referred to as adjuvants) encompass a category of medications that were not initially developed or used in pain management however, were found to be useful especially when combined with other categories of pain medications. These co analgesic medications include anticonvulsants, antidepressants, and topical anesthetics. With many of these agents, the onset of pain relief is delayed and analgesia may take weeks and requires dose escalations until acceptable pain relief is achieved (Stenstrom, and Larsson, 2011; Aiello-Laws, L et al., 2009). The research in the use and benefit of co analgesics in the cancer patient remains limited and further studies are needed (Vardy and Agar, 2014; Aiello-Laws, et al., 2009).

Gabapentin, a drug developed as an antiepileptic drug is an example of a co analgesic. The pharmacologic mechanism of action is unclear however it is theorized that it acts by

reducing the neurotransmitter release and attenuation of postsynaptic excitability in the spinal cord through inhibition of calcium currents by means the high voltage calcium ion channels. Gabapentin is not protein bound in the blood stream and is excreted through the renal system (Dooley, 2007). For this reason, patients with impaired renal function are recommended to be started at a lower dose and titrated slowly. The most common side effects include somnolence, dizziness, ataxia, edema, weight gain, dyspepsia, and leukopenia. Generally, patients are started on three divided doses of 300mg daily and are gradually increased every two to three days. Older adults may require lower dosing or slower titration since they are more likely to have a variety of physiologic changes that can alter absorption and pharmacokinetics. Older patients also require particular attention to other concomitant medications they may be taking with similar side effects as polypharmacy is common in this age group. Several weeks may be required to reach therapeutic levels and adequate therefore patients must have an understanding of the importance of compliance and reporting side effects to the clinician (Dworkin, 2007; Brant, 2010).

A computer search using CINHALL was conducted by a senior reference librarian. Relevant articles using CINHALL and PubMed data bases were queried with search terms gabapentin and oral mucositis from January 2010 to October 2015. One additional retrospective article that was submitted for publication in 2009 was included in light of its particular relevance. The selected articles were briefly screened for relevance and included in this review. Presently there are no systematic reviews of the specific use of gabapentin for neuropathic pain in radiation induced oral mucositis. A total of eleven references were obtained. Three retrospective studies were included in this review.

In 2010, a study published in *Head and Neck* (Bar Ad, V. B. et al., 2010) examined the role of gabapentin to treat the neuropathic pain syndrome in radiation induced OM. This retrospective study evaluated the effectiveness of gabapentin as a co analgesic in patients undergoing intensity modulated radiation therapy (IMRT) to the head and neck. A total of 29 patients treated at the Department of Radiation Oncology, University of Pennsylvania were included in the data analysis. All of the patients had undergone surgery and were treated with radiation in the postoperative setting from 2004 – 2006. No patients in this study received concurrent or induction chemotherapy. Two patients who received concurrent cetuximab were included in this sample. The patients were started on gabapentin during the second week of treatment at a dose of 600mg at bedtime and gradually titrated over one week to three daily doses of 900 mg with a total daily dose of 2700 mg. The study found that despite having grade 2 or higher OM during the third and fourth weeks of radiation treatment, only 10% required additional narcotic pain medications. During the final weeks of treatment, 35% required additional narcotics despite the presence of grade 2 or higher OM in 80% of cases. Two patients had interruptions in treatment of > 3 days however these interruptions were unrelated to radiation treatment toxicity.

Following these promising results, another retrospective study (Bar Ad, V.B, et al., 2010) was conducted by the same team, this time, examining patients who were undergoing concurrent IMRT and chemotherapy for head and neck cancers was performed. The sample consisted of 42 patients with head and neck cancer undergoing concurrent chemoradiation between December 2003 and November 2006 at the Department of Radiation Oncology at

the University of Pennsylvania. The patients were started on Gabapentin with the same titration schedule with a median dose of 2700 mg daily. During -week 1 and 2 of treatment, 88% (37) patients developed grade 1 or 2 OM. Thirty three percent and 55% of patients required additional low dose narcotic medications during the third and fourth weeks of treatment respectively despite exhibiting a grade 2 or higher OM in 71% (3rd week) and 86% (4th week). During the final weeks (week 5 and 6) of treatment, 71% of patients required additional low dose opiates for adequate pain control, despite the presence of grade 2 or higher OM in 95% and 100% of patients respectively. In this sample, one patient had a treatment break of > 3 days during treatment. (Bar Ad, et. al., 2010). Based on these studies, various cancer centers have adopted the use of gabapentin to treat pain syndromes in head and neck patients undergoing RT.

In 2014, a study published in *Dysphagia* expanded on these findings and retrospectively examined the impact of gabapentin on swallowing and feeding tube use during chemoradiation for oropharyngeal squamous cell carcinoma. This was a retrospective study of 23 patients using historical controls matched for stage. These patients underwent prophylactic PEG tube placement as standard of care in this institution. Patients were started on gabapentin prophylactically during the first week of radiation treatment. Patients treated with gabapentin began using their PEG tubes at a later date (3.7 vs 2.29 weeks) and had their PEG tubes removed earlier (7.29 vs 32.56 weeks). This difference was attributed to improved pain control allowing patients to maintain normal physiologic swallowing mechanisms for a greater amount of time during and after RT.

Implications for Nursing Practice

Oral mucositis and pain are both nursing sensitive outcomes. Nursing sensitive outcomes refer to those outcomes that are significantly impacted by interventions within the scope of nursing practice (Aiello-Laws, et al, 2009; Harris, D.J., et al., 2008). The use of evidence based management of symptoms in the oncology patient population has the promise of improving patient outcomes overall, promote patient and clinician satisfaction, and reduce costs to the health care system (Schulmeister, L, et al; 2008).

The identification of mixed neuropathic and nociceptive pain in the patient with head and neck cancer and OM from treatment has provided additional directions for pain management with the use of co analgesics. The use of gabapentin shows promise in managing the neuropathic pain component from OM.

Nursing considerations in the use of gabapentin include patient education regarding the titration and side effects including dizziness, somnolence ataxia and leukopenia.. Patients with compromised renal function and older adults require consideration of starting gabapentin at lower doses and slower titration. Older adults in particular are at increased risk for polypharmacy and require particular attention

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Figure 1. Head and Neck Cancer Regions

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Figure 2. A Five-Phase Model Proposed to Characterize Major Steps in Development and Resolution of Oral Mucositis

Note. With permission from Springer Science+Business Media: European Archives of Oto-Rhino-Laryngology, Radiation induced oral mucositis: A review of current literature on prevention and management, 27, 2016, p. 2,286, S. Mallick, R. Benson, & G.K. Rath, Figure 1.

Table 1
Common Terminology Criteria for Adverse Events for Oral Mucositis

Grade	Description
0	No oral lesions or discomfort
1	Asymptomatic or mild symptoms
2	Moderate pain; not interfering with oral intake; modified diet indicated
3	Severe pain; interfering with oral intake
4	Life-threatening consequences; urgent intervention indicated

Note: From Common Terminology Criteria for Adverse Events [v.4.0], by National Cancer Institute Cancer Therapy Evaluation Program, 2009.
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