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Randomized trial of standard pain control with or without gabapentin for pain related to radiation-induced mucositis in head and neck cancer

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ABSTRACT

Objective: Radiation-induced mucositis (RIM) in chemoradiotherapy (CRT) for head and neck cancer (HNC) causes severe pain and worsens CRT compliance, QOL and outcome. Following retrospective reports, we conducted a randomized trial of the safety and efficacy of gabapentin for RIM-associated pain during CRT.

Methods: HNC patients (pts) receiving CRT were randomized to standard pain control (SPC) with acetaminophen and opioids, or SPC plus gabapentin (SPC + G). Gabapentin was maintained at 900 mg/day for 4 weeks after CRT. Primary endpoint was maximum visual analogue scale (VAS) score during CRT, and secondary endpoints were total opioid dose, changes in QOL (EORTC QLQ-C30 and QLQ-HN 35) from baseline to 4 weeks after CRT, and adverse events.

Results: Twenty-two eligible Stage III or IV pts were randomly assigned to SPC or SPC + G ($n = 11$ each). Twelve were treated in a locally advanced setting and 10 in a postoperative setting. Median maximum VAS scores, median total dose of opioids at maximum VAS and total dose of opioids at 4 weeks after CRT tended to be higher in the SPC + G arm (47 in SPC vs. 74 in SPC + G, $p = 0.517$; 215 mg vs. 745.3 mg, $p = 0.880$; and 1260 mg vs. 1537.5 mg, $p = 0.9438$, respectively), without significance. QOL analysis showed significantly worse scores in the SPC + G arm for weight gain ($p = 0.005$). Adverse events related to gabapentin were manageable.

Conclusions: This pilot study is the first prospective randomized trial of gabapentin for RIM-related pain. Gabapentin had no apparent beneficial effect. Further research into agents for RIM-related pain is warranted.

1. Introduction

Patients undergoing radiotherapy (RT) for head and neck cancer (HNC) develop painful and debilitating mucositis. This often results in decreased oral intake, weight loss, decreased

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quality of life, and unforeseen treatment interruptions [1,2]. Further, this oral mucositis is significantly more frequent, severe, and of longer duration in patients undergoing concurrent chemoradiotherapy (CRT) [1]. The pathogenesis of radiation-induced mucositis (RIM) is multifactorial and appears to be more complex than direct damage to the epithelium [3,4]. Indeed, recent studies have demonstrated that HNC patients experience both nociceptive and neuropathic pain during their RT course, suggesting the need to treat both types of pain [5]. However, no suitable agents for the relief of this type of pain have yet been identified.

RIM-associated pain may respond symptomatically to oral rinses or systemic opioid therapy, and limited evidence suggests that some agents (GM-CSF, immunoglobulin, benzydamine, or vitamin E) may address the underlying mucositis [6–9]. The ideal strategy would be to prevent the development of mucositis, and thereby maintain locoregional tumor control without inducing greater RT toxicity, but few agents have shown substantial efficacy in preventing mucositis in HNC [2,10]. Thus, we generally prescribe non-steroidal anti-inflammatory drugs or acetaminophen, and morphine for mucositis-related pain in accordance with the WHO analgesia ladder. As a further complication, the effect of adjuvant drugs on neuropathic and nociceptive pain is also unknown.

The pain of RIM may be due to tissue damage from radiation, including ulceration and inflammation [11]. The International Association for the Study of Pain (IASP) defines neuropathic pain as pain initiated or caused by a primary lesion or dysfunction in the nervous system, resulting in debilitating pain [12]. Damage to somatic neurons commonly associated with nociceptive pain may result in neuropathic pain. This nervous system dysfunction may be exacerbated by persistent unrelieved nociceptive pain associated with radiation, producing additional neuropathic pain. Alteration in pain processing at the peripheral site (mucositis) and central levels (which may occur when mucositis pain is persistent) produces characteristic sensory abnormalities such as hyperalgesia and allodynia [13]. In a recent study, investigators identified pain in 56% of patients with HNC at diagnosis, among whom 93% had mixed nociceptive and neuropathic pain [14]. Although morphine has been considered the standard treatment for this acute pain syndrome related to RIM in patients with HNC [15], nociceptive and neuropathic pain respond poorly to opioids, and consequently require escalating doses [5].

Gabapentin is effective against a number of neuropathic pain syndromes, including chronic pain, diabetic neuropathy, post-herpetic neuralgia, trigeminal neuralgia, and postoperative pain [16,17]. Recent studies have demonstrated the efficacy of gabapentin in improving pain control in patients with neuropathic cancer pain who have already been treated with opiates [18]. Moreover, two retrospective studies in patients with HNC undergoing CRT [19,20] suggested that gabapentin was promising in reducing total doses of opioids and avoiding unplanned treatment interruptions. However, gabapentin has not been prospectively evaluated in these patients.

Here, we conducted a prospective randomized trial to compare standard pain control with or without gabapentin for pain related to RIM during radiation therapy for HNC.

2. Materials and methods

2.1. Study design

The study was conducted at a single center under an open label, prospective, randomized design. HNC patients were randomly assigned to receive either standard pain control (SPC) or SPC with gabapentin (SPC + G) during CRT. The study was registered in the UMIN-CTR as ID no. 000003012. The study protocol was approved by the institutional protocol review committee of Kobe University Hospital before the enrollment of any patients in the trial.

2.2. Patients and randomization

From April 2010 to October 2011, 22 eligible patients were randomly assigned to receive SPC ($n = 11$) or SPC + G ($n = 11$) at a 1:1 ratio. Computer-assisted randomization without stratification was used. Eligibility criteria were: (i) age 20 years and over; (ii) PS (ECOG) 0–2; (iii) pathologically proven HNC; (iv) primary site in the oral cavity, nasopharynx, oropharynx, hypopharynx, or larynx; (v) treatment with RT or CRT; (vi) planned total dose of RT $\geq$60 Gy; (vii) concurrent chemotherapy with cisplatin; and (viii) written informed consent. Exclusion criteria were: (i) active other malignancy; (ii) pregnant or breast feeding; (iii) mental disorder; (iv) continuous treatment with systemic steroids; (v) uncontrolled diabetes; (vi) cardiovascular disease within 3 months before registration; (vii) severe active comorbidities; (viii) history of severe hypersensitivity to anticonvulsants; (ix) renal dysfunction (creatinine clearance <60 mL/min.); (x) liver dysfunction (total bilirubin >2.0 mg/dL); (xi) active infection; (xii) use of anticonvulsants or antidepressants; (xiii) use of pain killers before starting radiation therapy; and (xiv) VAS over 4.0 before starting radiation therapy.

2.3. Radiation treatment and chemotherapy

In the locally advanced setting, RT planning was as follows [21]. Concomitant radiation treatment with 4 MV was administered at 2 Gy/day on 5 days/week for 7 weeks. In the locally advanced setting, RT planning was as follows. Gross tumor volume (GTV) was determined as the region judged on endoscopic and radiographic examination to contain the gross primary tumor or metastatic lymph nodes. Clinical target volume (CTV) was defined as the GTV plus volumes considered at risk of containing microscopic disease. The CTV was further categorized into two volumes, a CTV boost (CTVb), which included the primary tumor with a 1-cm margin craniocaudally and any metastatic nodes with a 0.5- to 2-cm margin; and a CTV subclinical (CTVs), which included the CTVb plus regional nodes. The CTVs was treated with 50 Gy by the multiple field technique or lateral opposed beams with a wedge filter. A booster dose of 20 Gy was given to the CTVb using the multiple field technique and electron beams to shield the spinal cord for a total dose of 70 Gy. In the postoperative setting, RT planning was as follows [22]. All patients underwent radiation therapy within 8 weeks after definitive surgery, consisting of conventionally fractionated doses of 2 Gy

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