Original Article

Preliminary study of therapeutic effect of parecoxib on severe radiation mucositis and dermatitis

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Background: Pain and inflammatory lesions are the main symptom and sign of radiotherapy (RT)-induced severe mucositis and dermatitis (RISMAD). Simultaneous treatment for pain and inflammation of RISMAD remains unsatisfactory. We collected the therapeutic information of parecoxib, a cyclooxygenase-2 (COX-2) inhibitor, on RISMAD in clinical observation.

Methods: A cohort of 11 cancer patients underwent radiotherapy between 2016 to 2020 was retrospectively analyzed. Intensity modulated RT was delivered by linear accelerators with various fractionation. Patients with grade 3 or 4 RISMAD and pain were treated by short-term daily administration of parecoxib via intramuscular injection. Severity of the symptoms was graded with CTCAE 4.0.

Results: Total eleven lesions were treated and analyzed. The incidence of mucositis, dermatitis and pain were 90.9%, 54.5% and 63.6% respectively. For patients with grade 3 or 4 mucositis and dermatitis, all the cases improved to grade 1 after receiving parecoxib (mucositis: 60% *vs.* 0%, P<0.001, dermatitis: 50% *vs.* 0%, P<0.001). Pain score improved from 5.8 to 0.9 (P<0.001) by visual analogue scale. Time to improvement for dermatitis, mucositis and pain was 6.3±3.1, 10.2±6.9 and 7.5±5.1 days, respectively. The average dose of parecoxib needed for improvement was 40 mg per day for 3.8±2.0 days. During the treatment and follow-up, there was no significant adverse effects noted in this cohort, such as skin rash, gastrointestinal bleeding, altered platelet function or cardiac events.

Conclusions: Parecoxib appears to be a safe and effective agent for managing severe RT induced mucositis, dermatitis and accompanied pain.

Keywords: Parecoxib; mucositis; dermatitis; nonsteroidal anti-inflammatory drugs (NSAIDs); cyclooxygenase-2 (COX-2) inhibitor

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Introduction

In recent decades, concurrent chemoradiation (CCRT) has been widely accepted in treatment of multiple cancer sites, including those of head and neck and pelvis. Growing evidence showed clinical benefit of CCRT which might be a result as of the following rationales: radiosensitization by chemotherapeutics, advances in radiotherapy (RT) technologies and improvement in toxicity care. Especially,

rationales supporting adding chemotherapy to radiation other than radiosensitization include enhancing local control, and potentially eliminating metastasis (1). Besides, chemotherapeutics, targeted therapeutic agents, such as epidermal growth factor receptor (EGFR) inhibitors, has been reported beneficial in control of locally advanced head and neck cancers while combined with RT. One phase III study has shown advantages of concurrent cetuximab and RT compared to RT alone in locally advanced head and neck cancer in locoregional control, progression free survival and overall survival (2), but the combination regimen enhanced toxicity and resulted in lower compliance and delay in completing RT course (3).

The mean incidence of mucositis in patient treated with CCRT or RT alone was 80%, and 34–57% with severity up to grade 3–4 (4). With concurrent chemotherapy, the risk of grade 3 oral mucositis increased about 4-fold over RT alone (5). Symptoms of mucositis can be relieved with topical anesthetics or opioid analgesics. Radiation-induced dermatitis are seen in 95% of patients (6) even in the era of intensity modulated RT (IMRT) to head and neck cancer. The side effects usually develop parallel to mucositis around 2–3 weeks after starting treatment with symptomatic progression near the end of treatment (7). As for RT to pelvic malignancy, such as cervical cancer, anal cancer and rectal cancer, the radiation dermatitis and mucositis are commonly noted due to inhomogeneous radiation dose distribution to perineal skin. For example, in cervical cancer treated with CCRT and high-dose rate brachytherapy, 23.9% patients developed grade 3 or higher diarrhea as one presentations of gastrointestinal mucositis, and 23.5% of grade 3–4 vulva skin dermatitis (8). Early soft tissue reaction for pelvic RT also starts at 2–3 weeks following initiation of the treatment. Management of the condition usually contains topical moisturizing cream or sitz bath and wound care with appropriate dressing. Oral or intravenous antibiotics may be required in severe cases, and analgesic for grade 3 or greater toxicity warrants assessment for a potential treatment threat. However, the management of RT-induced severe mucositis and dermatitis (RISMAD) and pain remain unsatisfactory.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most used medications in managing acute pain and inflammation, with cyclooxygenase (COX) enzyme being the major target of NSAIDs (9). Cyclooxygenase-2 (COX-2) can be induced endogenously and exogenously to various stimulation, including IL-1, IL-6, TNF-α or LPS, and stress. PGE_2 is the major metabolic product of COX-2 and elevated PGE_2 level along with other prostaglandin increases vascular permeability, lowers the threshold of pain and induces pain by sensitizing nerve ending in both central and peripheral nervous system, which results in an inflammatory response (10). COX-1 on the other hand is associated with metabolic products that have correlation with initiation of acute inflammatory response while COX-2 is responsible for maintaining the inflammatory process (11). Since the inhibition of COX-1 is related to adverse events in GI tracts, selective COX-2 inhibitors are better tolerated than non-selective NSAIDs but with comparable analgesic efficacy (9,12). Administration of steroid is effective in eliminating inflammatory reactions, but the adverse effects and inability to control pain limit its clinical application. Taken together, for RISMAD with pain, the optimal agents might be those capable in both anti-inflammation and pain relief without major toxicity, such as COX-2 inhibitors.

For patients suffering from severe oral mucositis who are unable to swallow, intravenous or intramuscular administration may be better preferred. Among cox-2 inhibitors, parecoxib could be delivered intramuscularly or intravenously with satisfying efficacy in pain relief, short time to onset and long lasting duration(13,14), In addition, it does not interfere with platelet function in either healthy elderly or non-elderly individuals (15), and is well tolerated by healthy elders at risk of upper gastrointestinal mucosal injury (16). Parecoxib can successfully help reduce opioid use in patients suffering from pain (17). In this preliminary study we evaluated the efficacy and side effect of parecoxib on managing RT-related inflammation and induced pain. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/tro-20-46).

Methods

Patients and identification

Data were retrospectively collected from January 2016 to May 2020 in cancer patients treated with RT with or without concurrent systemic therapy experiencing radiation induced dermatitis or mucositis at our institute who received parecoxib injection. Majority of the subjects had been treated with non-selective COX inhibitors, steroids and/or opioids without significant improvement before administration of parecoxib. The patients were evaluated weekly during the RT treatment by the attending radiation oncologist with record of the RT-related toxicity and dose

and response of parecoxib. Medical records included cancer diagnosis and stage, systemic therapy regimen, age at the time of treatment, acute toxicity, and its management. The patients' subjective sensation of irritation, pain or burning of the lesion were defined by patient's themselves using Visual Analogue scale (VAS) from 0 to 10, meaning no symptoms or worst. The study was approved by MacKay Memorial Hospital Institution Review Board (Approval Number: 20MMHIS195e) and conducted in accordance with the Declaration of Helsinki (as revised in 2013). For the study only involving retrospectively reviewing medical records, informed consent was not required under the approval of Mackay Memorial Hospital IRB.

Treatment

Patients were treated with IMRT with linear accelerator with various fraction size, including photon or electron beam. Total dose depended on the treatment guidelines or other special consideration with altered fractionation such as aggressive histology. Patients all received education of initial skin care and side effects management. When the patients developed grade 3 to 4 skin and mucosa reactions and failed to respond to non-selective COX inhibitors, steroids and/or opioids, parecoxib was prescribed with 40 mg per day via intramuscular route for 3 to 4 days consecutively in one week. The attending physician would evaluate the response to the treatment along with patient reported outcome and decide whether if administering next course of parecoxib is needed.

Response evaluation for parecoxib

Objectively, during the weekly examination, RT toxicities including mucositis and dermatitis were recorded and graded as recommended by CTCAE 4.0 (common terminology criteria for adverse event version). Subjective pain score was estimated by using VAS (visual analogue scale) reported by patients.

Statistical analysis

Descriptive analysis was first performed for categorical demographics, tumor and symptom characteristics. Paired-*t* test was used for analyzing symptom improvement after intervention. *P* values <0.05 were considered statistically significant. Analysis was performed by IBM SPSS software version 25 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

Patient's characteristics underwent RT are presented in *Table 1*. Between January 2017 to May 2020, there were total 11 patients who received parecoxib for management of radiation induced toxicities for various cancer and histology types. Of them, 7 patients were male (64%) and 4 were female (36%). The patients' median age of 64 years (range, 47–83 years), with all in good performance (ECOG 0-2). Most of them (81.8%) received higher radiation dose of greater than 60 Gy.

Result of efficacy

Total eleven lesions were treated, among the patients there were 7 (63.6%) treated with CCRT and 4 (36.4%) received RT alone. There incidence of mucositis, dermatitis and severe pain were 90.9%, 54.5% and 63.6% respectively. After receiving parecoxib, the improvements were significant in decreasing the severity of the symptoms. Before treatment, most patients had Grade 3 or higher mucositis and dermatitis, and all improved to Grade 1 after receiving parecoxib (mucositis: 60% *vs.* 0%, P<0.001, dermatitis: 50% *vs.* 0%, P<0.001) (*Figure 1A,B*). As for pain score, the average pain score before treatment was 5.8, and improved to 0.9 after receiving parecoxib (P<0.001) (*Figure 1C*).

We also evaluated the time to improvement for dermatitis and mucositis, which was defined as the time interval for symptoms returning to grade 1. As for pain score, time to improvement was defined as VAS decreasing to less than 4, commonly known as no pain with no intervention required. Time to improvement for dermatitis, mucositis and pain was 6.3±3.1, 10.2±6.9 and 7.5±5.1 days, respectively. The average dose of parecoxib needed for improvement was 40mg per day for 3.8±2.0 days (total dose 152 mg). During the treatment and follow-up, there was no significant adverse effects noted in this cohort, such as skin rash, gastrointestinal bleeding, altered platelet function or cardiac events (*Figure 2*).

Discussion

In this preliminary study, parecoxib appears to be a safe and effective agent for managing RT induced mucositis, dermatitis and accompanied pain. Comparing with historical data, we had similar incidence of toxicity of grade

Table 1 Patients characteristics

Patient characteristics	Numbers (%)
Age	
<50 years	3 (27.3)
≥50 years	8 (72.7)
Median (years)	64
Mean ± SD	62±13.5
Range (years)	47–83
Gender	
Male	7 (63.6)
Female	4 (36.4)
ECOG	
0–2	11 (100.0)
3–4	0 (0.0)
Locations	
Head and neck	8 (72.7)
Gynecology	1 (9.1)
Gastrointestinal	2 (18.2)
CCRT	
Yes	7 (63.6)
No	4 (36.4)
Radiation dose (Gy)	
<50	1 (9.1)
50–60	1 (9.1)
>60	9 (81.8)
Symptoms (incidence)	
Dermatitis	6 (54.5)
Mucositis	10 (90.9)
Diarrhea	1 (9.1)
Severe Pain (VAS >5)	7 (63.6)
Grade	
1	5 (45.5)
2	3 (27.3)
3	6 (54.5)
4	2 (18.2)

CCRT, concurrent chemoradiation.

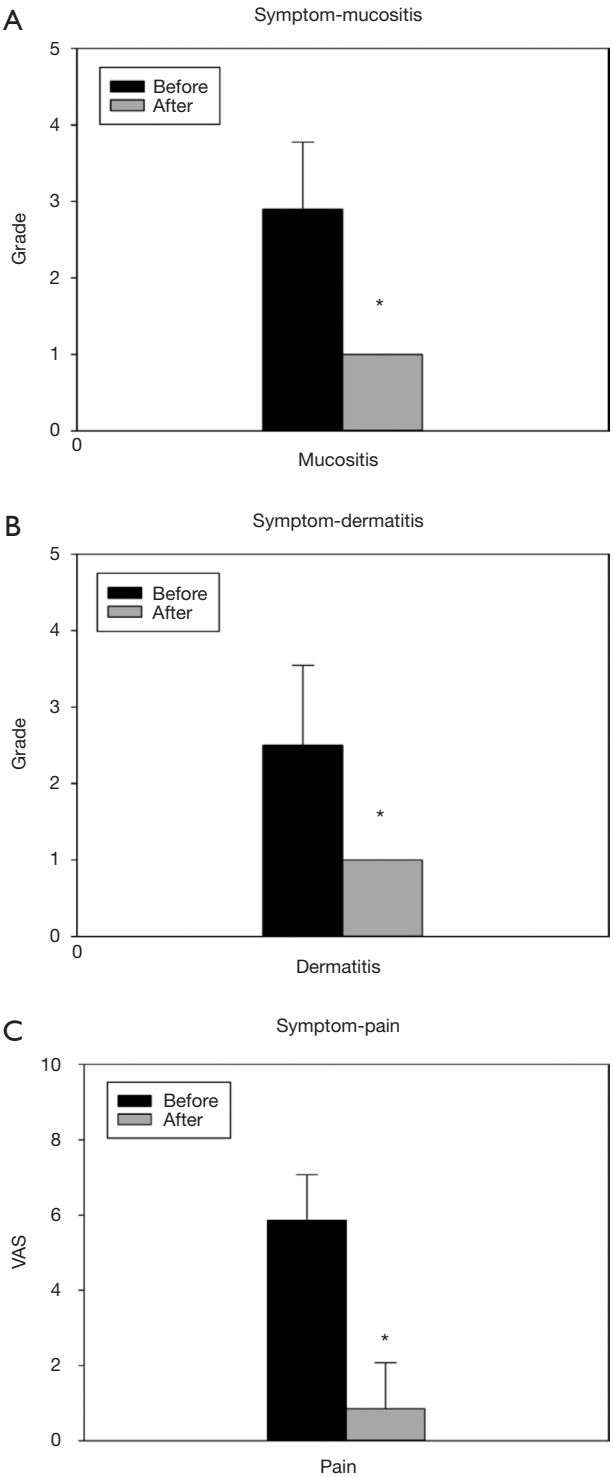

Figure 1 The severity of symptoms of interest were graded with CTCAE 4.0. (A) Mucositis, (B) dermatitis, (C) severe pain. All the above symptoms showed significant improvement after administering parecoxib. *, P<0.05.

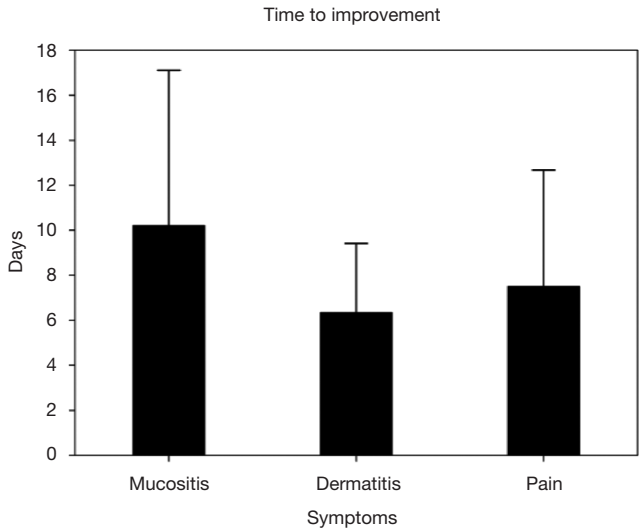

Figure 2 Time to improvement with treatment of parecoxib.

3–4 for either RT alone or CCRT (4). After administering parecoxib, the severity and duration of the symptoms also significantly improved compared to topical treatment (18).

Radiation-induced soft tissue injury, such as RISMAD in this study, has been termed as a "complex wound" because it involves structural damage mediated by groups of free radicals related to DNA damage, and alteration of normal cellular component of functional and structural proteins. Radiation not only interferes with normal maturation, reproduction, and repopulation of epidermal cells, but also targets fibroblast and vasculature (19). Each exposure to radiation leads to inflammatory cell aggregation and direct tissue damage with further impairment of healing by normal tissue (20). Acute radiation injury is a combination of reduced functions of stem cells, inflammation, and epidermal cell necrosis and apoptosis (21).

The mechanism associated with radiation induced skin reaction includes inflammatory response and oxidative stress. After radiation induced cell damage, cells die especially in the form of mitotic death. Late in chronic phase, inflammation and oxidative stress would cause various cytokines, cell cycles, and DNA changes, which sustaining the cascade and lead to late reaction (22). In the initial response, immediately generated inflammatory response is mainly caused by pro-inflammatory cytokines, such as IL-1, IL-3, IL-5 , IL-6 and tumor necrosis factor (TNF)-α, chemokines, receptor tyrosine kinase, and adhesion molecules (23). Among them, IL-1 plays an important role in modulating RT induced skin response as shown in mice lacking IL-1 production or receptor develop less inflammation and pathologic changes skin (24). In addition, both IL-1 and TNF-α are involved in inducing COX-2 expression (25,26).

RT induced dermatitis and mucositis are severe and common complications due to loss of stem cells in the basal layer, compromising the replacement of cells when sloughing. This subsequent denuding leads to mucositis which results in pain and interferes with patient's oral intake of nutrition and daily life. Severe mucositis may lead to 11% unplanned interruption of treatment, thereby compromising treatment efficacy and patient survival (4). Mucositis also occurs distal to the oropharyngeal cavity along the alimentary tract. When presenting as gastrointestinal mucositis it is commonly known as enteritis or proctitis. Further gastrointestinal mucosal ulceration could lead to perforation, fistula, or abscess formation. Even when the ulcers heal, there could be fibrosis with narrowing of the lumen or obstruction (27). Steroids are well-known for its ability to inhibit all kinds of inflammation, therefore widely used in managing radiation dermatitis and mucositis. With the help of betamethasone, the skin reaction of breast cancer patient receiving adjuvant RT is significantly decreased (28). In patients receiving beclomethasone supplement during radiotherapy treatment, rectal bleeding was reduced but no significant improvement in bowel symptoms at 3 or 12 months (29). Steroids are also known to prolong the treatment time for skin care since they may damage skin's integrity and result in possible further adverse effects which is not suitable for long term use (30). Low dose steroids with equal or greater than 5 mg/d would also lead to several adverse events such as gastrointestinal bleed or ulcer, infection or fractures (31).

For more specific anti-inflammatory and pain control effect comparing to steroid use, COX inhibitor has excellent anti-inflammatory capacity and pain management allowing reduction in use of opioids (32). In managing mucositis in patients receiving RT dose >50 Gy, benzydamine improved grade 3 mucositis from 62.1% to 36.4%, with reduction in needs of tube feeding, intravenous supplementations (18). Although there were benefits in reducing the severity of mucositis using benzydamine, there was no significant difference in analgesic effect from pain scores comparing the use of sodium bicarbonate alone (33).

Selective COX-2 inhibitor has been shown to reduce skin damage after radiation not only by decreasing production of PGE and PGF2α to tone down the extent

of inflammation, but also decreased chemokine mRNA expression in skin tissue, and down-regulate infiltration of monocytes and neutrophils (34). Due to increased COX-2 activity amplifying radiation toxicity in the irradiated area and adjacent normal tissue, increased COX-2 expression in the distant non-irradiated area also increased oxidative stress and DNA damage which may upregulate cancer risk. Activation of COX-2 can enhance resistance of malignant cell to radiotherapy. Hence, inhibition of COX-2 has been proposed for better therapeutic gain and normal tissue amelioration (35). Other RT-related complication such as RT induced neuroinflammation is also found to be associated with an elevation of COX-2 expression and accompanied by increase of PGE2. RT induced changes in vascular permeability is dependent on COX-2 activity, implicating this protein as target for potential therapeutic role in managing side effects on radiation of normal brain tissue (36).

Since it is equipotent comparing with non-selective NSAIDs such as diclofenac but with less undesirable side effects, it would seem more preferable to prescribe selective COX-2 inhibitor (37). Among COX-2 inhibitors, celecoxib is the most studied agent. Though in practice celecoxib showed limited benefits in reducing severity of oral mucositis for head and neck cancer patient (38) or preventing skin toxicity in breast cancer receiving RT (39), there was slight improvement in T-downstaging and N-downstaging for locally advanced rectal cancer (40). Parecoxib, a novel COX-2 inhibitor possessing better pain control (41), also has greater anti-tumor potency than celecoxib (42). In elderly subjects, parecoxib is safe and well tolerated even in multiple dose administration has a decreased risk of gastrointestinal mucosal injury compared to ketorolac (16).

The efficacy of parecoxib on improving pain and RISMAD was evident with a rapid response. The limitations of this study include small sample size and retrospective observation. Based on this preliminary investigation, further study may be designed and carried out for proving its superiority in control of RT-induced mucositis and dermatitis as well as related pain.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tro-20-46). Yu-Jen Chen serves as an Editor-in-Chief of *Therapeutic Radiology and Oncology*. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by MacKay Memorial Hospital Institution Review Board (Approval Number: 20MMHIS195e). For the study only involving retrospectively reviewing medical records, informed consent was not required under the approval of Mackay Memorial Hospital IRB.

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