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Original Research Article

The association between diarrhea and serum cytokines in patients with gynecologic cancer treated with surgery and pelvic chemoradiotherapy

Keun-Yong Eom [a,*], Chan Woo Wee [a], Changhoon Song [a], In Ah Kim [a], Jae-Sung Kim [a], Kidong Kim [b], Dong Hoon Suh [b], Jae Hong No [b], Yong Beom Kim [b], Jeong Su Park [c]

[a] Department of Radiation Oncology, Seoul National University Bundang Hospital, Seongnam, Republic of Korea
[b] Department of Obstetrics and Gynecology, Seoul National University Bundang Hospital, Seongnam, Republic of Korea
[c] Department of Laboratory Medicine, Seoul National University Bundang Hospital, Seongnam, Republic of Korea

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ABSTRACT

Purpose: We investigated whether serum cytokines including Interleukin (IL)-1β, IL-6 and tumor necrosis factor alpha (TNFα) are increased during pelvic chemoradiotherapy (CRT) in patients with gynecologic malignancies, and sought to identify prognostic factors for the development of diarrhea during pelvic CRT.

Materials and methods: Patients with cervical or endometrial cancer receiving postoperative pelvic CRT were eligible for this prospective study. Patients were evaluated weekly during CRT for symptoms, including diarrhea and constipation. Serum cytokine levels were measured using immunoassays 1 week before CRT, and at week 3 and 5–6 during CRT. Radiotherapy-related parameters such as mean dose, minimum dose, and maximum dose to the small bowel were also analyzed. Multivariate logistic regression analysis was used to assess factors associated with development of enteritis symptoms.

Results: Twenty-six patients were enrolled, all of whom were eligible for symptom and dosimetric parameter evaluation; 24 were eligible for cytokine level measurement. Cytokine levels did not differ between patients with and without diarrhea before CRT. IL-6 levels increased during CRT, and were significantly higher in patients with diarrhea ≥grade 2 than in those with grade 0–1 at week 5–6 (6.771 ± 2.657 pg/mL vs. 3.396 ± 0.499 pg/mL, $p = 0.046$). Serum IL-1β and TNFα levels did not change during CRT. Diarrhea before CRT and the maximum dose to the small bowel were independent prognostic factors for CRT-induced diarrhea in the multivariate analysis.

Conclusions: There was an increase of serum IL-6 levels in patients with ≥grade 2 diarrhea during pelvic CRT. Serum IL-1β and TNFα levels did not change during CRT. Radiotherapy-related and clinical factors affect the development of diarrhea during pelvic CRT.

1. Introduction

In patients with pelvic malignancies including rectal cancer, and gynecologic cancers, pelvic chemoradiotherapy (CRT) is often a part of the standard treatment either before or after radical surgery. Pelvic CRT reduces pelvic recurrence of malignancies, but induces acute enteritis, with a reported incidence of up to 90% [1]. The small bowel is inevitably within the radiation field during pelvic CRT, which result in treatment-related acute enteritis in patients with gynecologic cancers. Pelvic radiotherapy inevitably involves small intestine in radiation field that results in acute enteritis for patients with gynecologic cancers. The intestinal epithelium is sensitive to radiotherapy, and is vulnerable to radiation damage. Radiotherapy causes changes in the bowel characterized by inflammation and cell death including mucosal cell loss, acute inflammation in the lamina propria, eosinophilic crypt abscess formation and swelling of the endothelial lining of arterioles [2]. Radiotherapy parameters contribute to the development of acute enteritis in patients receiving pelvic CRT. In previous studies investigating the dose and volume effects of radiotherapy, the small bowel volume exposed to significant radiation and the mean and maximum doses to the small bowel were predictive of grade 2–3 acute enteritis [3–5].

Mucosal inflammation caused by radiotherapy affects several pathways in the inflammatory cascade, including nuclear factor kappa B (NF-kB) and signaling transducers and activators of transcription members

* Corresponding author at: Department of Radiation Oncology, Seoul National University Bundang Hospital, 82 Gumi-ro 173beon-gil, Bundang-gu, Seongnam 13620, Republic of Korea.
E-mail address: 978sarang@hanmail.net (K.-Y. Eom).

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[6]. NF-kB plays an important role in immune and inflammatory responses, as it regulates proinflammatory cytokines and chemokines, such as tumor necrosis factor alpha (TNFα), interleukin (IL)-1, IL-2, IL-6 and monocyte chemoattractant protein-1 [7]. Proinflammatory cytokines such as TNFα, IL-6, IL-1β, which are involved in inflammatory processes, offer positive feedback for this process. Upregulation of genes associated with radiation-induced transcription factor activation results in the production of proinflammatory cytokines, including TNFα, IL-1β, and IL-6 [8]. In animal studies, elevated expression of TNFα, and IL-1β have been shown in the buccal mucosa of hamsters treated with chemotherapy and radiotherapy [9]. However, it is unclear that those findings will be applied to humans.

Therefore, we investigated whether serum cytokines, including IL-1β, IL-6 and TNFα, are increased during pelvic CRT in patients with gynecologic malignancies and sought to identify prognostic factors for the development of diarrhea during pelvic CRT.

2. Patients and methods

2.1. Patient accrual

We prospectively enrolled 26 patients who were diagnosed of cervical or endometrial cancer. Patients underwent radical surgery and postoperative CRT between 2017 and 2020. Inclusion criteria were age 20–70 years, Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and postoperative CRT to the whole pelvis for 5–6 weeks with concurrent intravenous cisplatin. According to the institutional policies, most of patient with cervical cancer indicative of postoperative radiotherapy received pelvic CRT and some of patients with stage III-IV endometrial cancer received pelvic CRT followed by adjuvant chemotherapy. Exclusion criteria included history of other malignancies other than breast cancer, and thyroid cancer, acute or chronic inflammatory disease, ECOG performance status of 3–4, and administration of immunomodulators. All patients agreed to participate in this study and provided written informed consent. This study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (IRB number B-1601/330-308).

2.2. Pelvic CRT

Patients received pelvic CRT with weekly cisplatin after surgery. Computed tomography (CT)-based simulation was performed in the supine position. CT images were obtained and reconstructed with a slice thickness of 3–4 mm. The clinical target volume (CTV) included the vaginal cuff and pelvic lymph node area covering the obturator, internal iliac lymph nodes, external iliac lymph nodes, and presacral lymph nodes according to the Radiation Therapy Oncology Group guidelines. The small bowel volume was contoured at each CT slice from the lower margin of CTV to 2 cm above the upper margin of the CTV. Three-dimensional planning target volume (PTV) margin 5 mm was used. The prescribed radiation dose was 46 Gy with a daily dose of 2 Gy in 21 patients and 50.4 Gy with a daily dose of 1.8 Gy in 5 patients. Intensity-modulated radiotherapy were performed in 25 (96%) patients, and one patient received three-dimensional conformal radiotherapy. The concurrent chemotherapeutic regimen was weekly cisplatin 30–40 mg/m^2 for 3–6 cycles at the discretion of the treating physician. Most of patients (21/26, 81%) received 5 cycles of concurrent weekly cisplatin: three patients (12%) underwent 6 cycles, one patient (4%) did 3 cycles and the other (4%) did 4 cycles, respectively.

2.3. Acute enteritis evaluation

Before radiotherapy, patients were asked about symptoms related to diarrhea and constipation using the Common Terminology Criteria for Adverse Events (v4.0) (Suppl Fig. 1). During radiotherapy, patients' symptoms were evaluated weekly

2.4. Pro-inflammatory cytokines

Blood samples were obtained 3 times at 1 week before pelvic CRT, at week 3 and 5 during pelvic CRT. After 5 mL of whole blood were collected in serum separator tube, clotting was performed for 30 min at room temperature. Then, the mixture was centrifuged for 10 min with 3000 rpm. A volume of 1.5 mL of serum was transferred to a transfer tube, and stored at −70 °C.

Proinflammatory cytokine levels, including IL-1β, IL-6, TNFα, were measured twice using a human immunoassay kit (R&D System, MN, US) and averaged for further analysis. All blood samples were collected according to the protocol. Two patients with cervical cancer withdrew consent for blood sampling during radiotherapy. Thus, 24 patients were evaluated for proinflammatory cytokine levels.

2.5. Statistical analysis

T-test was performed to compare clinical variables affecting acute enteritis symptoms. Correlations between clinical variables were analyzed using Spearman's rank correlation coefficient (ρ). The Wilcoxon rank sum test and chi-square test were used as appropriate. Logistic regression was applied in the multivariate analysis. Statistical analyses were performed using IBM SPSS statistics (version 20; IBM, Chicago, IL). Statistical significance was set at $p < 0.05$.

3. Results

3.1. Patient characteristics

Twenty-one (81%) patients were diagnosed with cervical cancer, and five (19%) were diagnosed with endometrial cancer. The mean age of patients was 48.0 ± 9.0 years (range, 32–64). (Table 1). The mean volume of small bowel in the radiation field was 230.0 ± 104.4 mL

Table 1
Patient and treatment characteristics.

	N (%)	Range
Age		
Mean (years)	48	32–64
BMI		
Mean (Kg/m^2)	22.3	17.3–28.9
Primary site		
Cervix	21 (81)	
Endometrium	5 (19)	
RT technique		
3D-CRT	1 (4)	
IMRT	25 (96)	
Small bowel volume (cm^2)	230 ± 0.20	66.5–448.0
Prescribed dose (Gy)	46	46–50.4
Mean dose to small bowel (Gy)	27.5 ± 0.72	21.1–35.2
Maximum dose to small bowel (Gy)	50.0 ± 0.38	47.7–54.6
Minimum dose to small bowel (Gy)	4.81 ± 0.24	2.3–8.1
WBC count (x10^3 per μℓ)		
Before RT	6.85 ± 0.36	3.90–12.00
At week 3	4.71 ± 0.37	2.32–9.10
At week 5–6	3.35 ± 0.25	1.60–7.56
Platelet count (x10^3 per μℓ)		
Before RT	311 ± 88.4	275–346
At week 3	226 ± 58.0	202–250
At week 5–6	172 ± 65.4	145–198
Concurrent chemotherapy		
Weekly cisplatin 30–40 mg/m^2	26 (100)	
Cycles		
3	1 (4)	
4	1 (4)	
5	21 (81)	
6	3 (12)	

Abbreviation: BMI, body mass index; RT, radiotherapy; 3D-CRT, three dimensional conformal radiotherapy; IMRT, intensity modulated radiotherapy; WBC, white blood cell count.

(range, 66.5 – 448.0 mL), and the mean radiation dose to the small bowel was 27.5 ± 3.7 Gy (range, 21.1 – 35.2 Gy). White blood cell and platelet count decreased over the course of radiotherapy (both $p < 0.001$).

Age was related to the small bowel volume in the radiation field ($\rho = 0.418$, $p = 0.034$). Small bowel volumes receiving 5 Gy, 10 Gy, and 15 Gy were significantly positively correlated with age ($p = 0.032$, 0.025, and 0.027, respectively). However, in volumes receiving ≥ 15 Gy, this correlation was no longer significant. The mean radiation dose to the small bowel was not related to age ($\rho = 0.11$, $p = 0.959$).

3.2. Clinical symptoms including diarrhea and constipation

The incidences of diarrhea and constipation were significantly different before, at week 3, and at week 5–6 of pelvic CRT. The incidence of diarrhea increased and the incidence of constipation decreased as CRT progressed. (Table 2).

Regarding diarrhea, three patients (11.5%) had grade 1 diarrhea before pelvic CRT. None of the patients had grade ≥ 2 diarrhea. At week 3 of pelvic CRT, seven (26.9%) patients had grade 1, two (7.7%) had grade 2 diarrhea, and one (3.8%) had grade 3 diarrhea. At weeks 5–6 of pelvic CRT, ten (38.5%) had grade 1 and four (15.4%) had grade 2 diarrhea. (Table 2).

Regarding constipation, nine patients (34.6%) had grade 1 constipation before pelvic CRT. Another nine (34.6%) had grade 2 constipation. At week 3, three (11.5%) had grade 1, and five (19.2%) had grade 2 constipation. At weeks 5–6, two patients (7.7%) had grade 1 constipation, and three (11.5%) had grade 2 constipation.

3.3. Cytokine level and clinical symptoms

The mean levels of TNFα before CRT, after 3 weeks of CRT, and after 5–6 weeks of CRT were 1.038 ± 0.216 pg/mL, 1.015 ± 0.273 pg/mL, and 1.126 ± 0.272 pg/mL, respectively ($p = 0.949$). The corresponding levels for IL-1β were 0.405 ± 0.229 pg/mL, 0.321 ± 0.134 pg/mL, and 0.403 ± 0.108 pg/mL, respectively ($p = 0.845$), and those for IL-6 were 3.126 ± 0.554 pg/mL, 2.867 ± 0.525 pg/mL, and 3.818 ± 0.566 pg/mL, respectively ($p = 0.458$). The mean levels of TNFα, IL-1β and IL-6 in patients with diarrhea before CRT were 0.656 ± 0.323 pg/mL, 0.134 ± 0.009 pg/mL, and 3.386 ± 1.491 pg/mL, respectively. The corresponding levels of these cytokines in patients without diarrhea were 1.090 ± 0.241 pg/mL, 0.442 ± 0.260 pg/mL, and 3.091 ± 0.608 pg/mL, respectively. Before CRT, the mean cytokine levels did not differ between patients with and without diarrhea ($p = 0.333$ for TNFα, $p = 0.867$ for IL-1β, and $p = 0.250$ for IL-6, respectively). Although the mean levels of IL-1β and TNFα were lower in patients with grade 1 diarrhea than those without diarrhea, the difference was not statistically significant. In addition, the mean levels of IL-6 were not different between patients with and without diarrhea.

At week 3, the mean levels of TNFα, IL-1β and IL-6 in patients with diarrhea were 1.341 ± 0.662 pg/mL, 0.566 ± 0.336 pg/mL, and 4.205 ± 1.187 pg/mL, respectively. The corresponding levels of these cytokines in patients without diarrhea were 0.891 ± 0.214 pg/mL, 0.161 ± 0.022 pg/mL, and 1.931 ± 0.246 pg/mL, respectively. There was a trend of increased IL-6 (4.205 ± 1.187 pg/mL vs. 1.931 ± 0.246 pg/mL, $p = 0.095$) in patients with grade ≥ 1 diarrhea compared to those without diarrhea.

At weeks 5–6, the mean levels of TNFα, IL-1β and IL-6 in patients with diarrhea were 0.888 ± 0.180 pg/mL, 0.355 ± 0.087 pg/mL, and 4.006 ± 0.835 pg/mL, respectively. The corresponding levels of these cytokines in patients without diarrhea were 1.363 ± 0.518 pg/mL, 0.602 ± 0.361 pg/mL, and 3.631 ± 0.800 pg/mL, respectively. The mean level of IL-6 in patients with grade ≥2 diarrhea was greater than that in patients with grade 0–1 diarrhea (6.771 ± 2.657 pg/mL vs. 3.396 ± 0.499 pg/mL, $p = 0.046$) (Fig. 1). There was no difference in serum IL-1β or TNFα levels between patients with and without diarrhea. Regarding constipation, there was no significant difference in the mean cytokine levels between patients with and without constipation before or during radiotherapy (suppl table 1).

3.4. Prognostic factors for diarrhea and constipation

Diarrhea during pelvic CRT was significantly related to diarrhea before pelvic CRT. The ρ between diarrhea before pelvic CRT and diarrhea at week 3 and weeks 5–6 during pelvic CRT were 0.445 ($p = 0.023$) and 0.455 ($p = 0.02$), respectively. Likewise, the ρ between constipation before pelvic CRT and constipation at week 3 and weeks 5–6 during pelvic CRT were 0.632 ($p = 0.001$) and 0.474 ($p = 0.014$), respectively.

When the small bowel volume receiving a typical radiation dose was investigated in units of 5 Gy, V50 and Vmax were positively associated with diarrhea at 5–6 weeks during pelvic CRT ($\rho = 0.417$, $p = 0.034$ and $\rho = 0.446$, $p = 0.022$, respectively). The mean radiation dose to the small bowel and irradiated volumes receiving > 15 Gy were not related to the development of diarrhea. In multivariate logistic regression analysis, the development of diarrhea at weeks 5–6 was related to diarrhea before CRT ($p = 0.001$) and maximum dose ($p = 0.004$). The mean levels of cytokines were not related to the development of diarrhea at weeks 5–6.

4. Discussion

In this prospective study that recruited patients with gynecologic

Table 2
Incidence of diarrhea and constipation before and during radiotherapy.

	Before RT (%)	At week 3 (%)	At week 5–6 (%)	p
Diarrhea grade				0.037
0	23 (88.5)	16 (61.5)	12 (46.2)	
1	3 (11.5)	7 (26.9)	10 (38.5)	
2		2 (7.7)	4 (15.4)	
3		1 (3.8)		
Constipation grade				0.004
0	8 (30.8)	18 (69.2)	21 (80.1)	
1	9 (34.6)	3 (11.5)	2 (7.7)	
2	9 (34.6)	5 (19.2)	3 (11.5)	

Abbreviation: RT, radiotherapy.

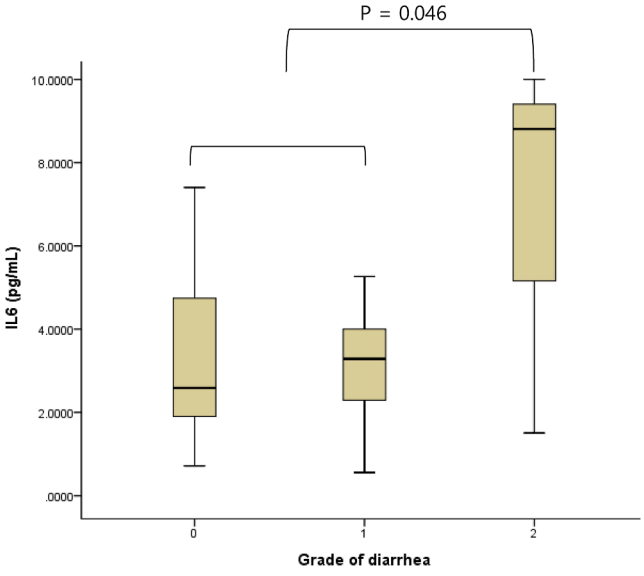

Fig. 1. The association of serum LL-6 levels and grade of diarrhea at week 5 during pelvic chemoradiotherapy. Data are expressed as the mean ± standard error of the mean.

cancer who were treated with radical surgery followed by pelvic CRT, serum IL-6 levels were significantly associated with grade ≥2 diarrhea at weeks 5–6 of CRT. There was no relationship between the levels of IL-1β and TNFα and the development of diarrhea. In addition, diarrhea before pelvic CRT was prognostic for the development of symptomatic diarrhea during CRT, as was the maximum dose to the small bowel, with statistical significance.

Proinflammatory cytokines have been previously implicated in radiation-induced gastrointestinal mucositis. IL-6 is an interleukin that acts as a pro-inflammatory cytokine. Several studies have shown that elevated IL-6 levels in the serum are associated with acute enteritis caused by pathogens and inflammatory bowel disease [10,11]. In a rat model, radiation-induced sub-acute damage was associated with significantly upregulated IL-1β, IL-6, and TNFα mRNA levels in the jejunum and colon [12]. Another study investigating the effect of radiotherapy on epithelial cells in the small bowel in rats found that IL-2 and IL-6 levels were significantly elevated in rats who received irradiation [13]. However, the relationship between radiation and IL-6 has not been well studied in humans. In a pilot study enrolling patients with prostate or rectal cancer, Hallemeier at al. examined IL-6 levels and transforming growth factor-β level and found no correlation of IL-6 levels with radiation enteritis or the small bowel volume receiving radiotherapy [14]. In contrast, Meirovitz et al. showed a positive correlation between serum IL-6 levels and the severity of mucositis and dysphagia in patients with head and neck cancer receiving CRT [15]. Similarly, this study revealed that serum IL-6 levels were associated with grade ≥2 diarrhea in weeks 5–6 of pelvic CRT in patients with gynecologic cancer.

Dysregulation of TNFα expression is thought to be involved in autoimmune diseases, including inflammatory bowel disease, rheumatoid arthritis, and ankylosing spondylitis [16]. However, its role in radiation-induced enteritis remains unclear. Although preclinical models demonstrate increased expression of TNFα and IL-1β in irradiated small bowels, the findings in human sample are controversial [17]. Meirovitz et al. found no significant change of TNFα or IL-1 levels in blood samples of patients with head and neck cancer receiving CRT [15]. Conversely, a trend of increased TNFα was observed in the saliva of a similar cohort of patients [18]. Additionally, Bossi et al. found an increase of IL-1β in the saliva of patients with head and neck cancer treated with radiotherapy [19]. In this study, serum TNFα and IL-1β level did not change significantly in patients receiving pelvic CRT, and neither was related to the development of diarrhea or constipation in these patients.

Radiotherapy parameters, such as the treated volume or the prescribed dose, are prognostic for the development of diarrhea. Letschert et al. demonstrated that there is a volume-effect in radiation-induced diarrhea at a dose of 50 Gy in 25 fractions in patients with rectal cancer [3]. A similar study reported by Gunnlaugsson et al. showed a strong correlation between the occurrence of grade ≥2 diarrhea and the irradiated small bowel volume, specifically at doses >15 Gy [4]. In this study, the maximum dose to the small bowel was an independent factor for the development of diarrhea at weeks 5–6 of pelvic CRT. The irradiated volumes receiving >15 Gy or the mean dose to the small bowel were not significant for the development of diarrhea in this study. The difference from previous studies could be explained by the difference in patient population and the radiotherapy technique. Previous studies enrolled patients with rectal cancers and used three-dimensional conformal radiotherapy which delivers much higher radiation to the small bowel than intensity-modulated radiotherapy does.

Several clinical factors are associated with the development of radiation-induced enteritis. Patients with risk factors such as diabetes, inflammatory bowel disease, low body mass index, and heavy smoking are susceptible to radiation-induced enteritis [20–22]. Diarrhea before pelvic CRT was another independent prognostic factor of diarrhea in this study. Patients experiencing diarrhea before pelvic CRT were significantly more likely to experience grade ≥2 diarrhea during pelvic CRT. Therefore, patients with diarrhea before pelvic CRT should be carefully evaluated and managed.

The limitation of this study is the small number of patients and the relatively long period of enrollment. Due to the slow accrual of patients in a single institution, this study was conducted for 4 years. However, this study enrolled homogenous patients with gynecologic malignancies treated with an advanced radiotherapy technique, intensity-modulated radiotherapy. To the best of our knowledge, this is the first study to reveal the relationship between clinical symptoms, including diarrhea and constipation, and serum cytokine levels in patients with gynecologic cancers who received pelvic CRT after radical surgery.

In summary, this study revealed a correlation of serum IL-6 levels and the development of diarrhea during pelvic CRT. Additionally, diarrhea before CRT and the maximum dose to the small bowel were independently prognostic factors for the development of diarrhea during pelvic CRT. However, this was a prospective study with small number of patients. Further studies enrolling a large number of patients are needed to confirm the findings of this study.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2021.05.010.

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