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Clinical Investigation

Can Angiotensin-Converting Enzyme Inhibitors Reduce the Incidence, Severity, and Duration of Radiation Proctitis?

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Summary

Using a propensity-score match analysis of 817 patients treated with radical radiation therapy with neoadjuvant or adjuvant hormone therapy as first-line management for prostate cancer, this study observed that patients who were taking angiotensin-converting enzyme inhibitors (ACEIs) were significantly less likely to have high-grade proctitis, and the ACEIs were also significantly associated with a reduced risk of radiation-induced proctitis and with acceleration of its resolution.

Purpose: To determine whether participants taking angiotensin-converting enzyme inhibitors (ACEIs) and treated with radical radiation therapy with neoadjuvant/adjuvant hormone therapy have less incidence, severity, and duration of radiation proctitis.

Methods and Materials: A propensity score analysis of 817 patients who underwent radical radiation therapy with neoadjuvant or adjuvant hormone therapy as primary line management in a cohort study during 2009 to 2013 was conducted. Patients were stratified as follows: group 1, hypertensive patients taking ACEIs (as a study group); group 2, nonhypertensive patients not taking ACEIs; and group 3, hypertensive patients not taking ACEIs (both as control groups). The incidence, severity, and duration of proctitis were the main outcome. χ^2 tests, Mann-Whitney *U* tests, analysis of variance, risk ratio (RR), confidence interval (CI), Kaplan-Meier plots, and log-rank tests were used.

Results: The mean age of the participants was 68.91 years, with a follow-up time of 3.38 years. Based on disease and age-matched comparison, there was a statistically significant difference of proctitis grading between the 3 groups: χ^2 (8, n = 308) = 72.52, $P<.001$. The Mann-Whitney *U* test indicated that grades of proctitis were significantly lower in hypertensive patients taking ACEIs than in nonhypertensive patients not taking ACEIs and hypertensive patients not taking ACEIs ($P<.001$). The risk ratio (RR) of proctitis in hypertensive patients taking ACEIs was significantly lower than in hypertensive patients not taking ACEIs (RR 0.40, 95% CI 0.30-0.53, $P<.001$) and in nonhypertensive patients not taking ACEIs (RR 0.58, 95% CI 0.44-0.77, $P<.001$). Time to event analysis revealed that hypertensive patients taking ACEIs were significantly different from the

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control groups ($P<.0001$). Furthermore, hypertensive patients taking ACEIs had significantly faster resolution of proctitis ($P<.0001$).

Conclusion: Patients who were taking ACEIs were significantly less likely to have high-grade proctitis after radical radiation therapy with neoadjuvant or adjuvant hormone therapy ($P<.001$). The intake of ACEIs was significantly associated with a reduced risk of radiation-induced proctitis and also with acceleration of its resolution.

Introduction

Since the introduction of prostate-specific antigen (PSA) testing in prostate cancer screening, more patients now receive earlier diagnoses and subsequently have undergone radical treatment (1). One option in the clinical management of prostate cancer is radical radiation therapy (2, 3). However, proctitis is an adverse event of radiation therapy to the prostate and can have a profound negative affect on patients' overall quality of life (4-7). The initial step of proctitis is cell death and cell depletion, leading to loss of the epithelium lining and, as a consequence, edema and mucosal inflammation, which later leads to ulceration and sepsis. By the time inflammation spreads to the submucosa and provokes a regenerative response, which in turn causes either normal tissue repair, or ulceration, fibrosis, and structuring, obliteration, fibrosis, and angiogenesis lead to the clinical manifestations of rectal bleeding, tenesmus, diarrhea, and strictures (8-11).

Experimental studies have shown that angiotensin-converting enzyme inhibitors (ACEIs) may prevent the development of radiation-induced injuries in certain tissues (12-14). ACEIs are antihypertensive drugs that block the enzyme and prevent the conversion of angiotensin I to angiotensin II, which plays an important role in controlling blood pressure. Previous studies have focused on the effect of ACEIs in the prevention of radiation-induced lung toxicity. Four animal studies conducted between 1988 and 2009 all reported consistent results of the protective effect of ACEIs in lung parenchyma, yielding beneficial outcomes in terms of reducing the incidence of radiation-induced pneumonitis (12-16). In lung cancer patients, 4 clinical studies have been conducted between 2000 and 2013 (14, 17-19). One study reported a beneficial effect of ACEIs ($n=146$) in preventing radiation-induced lung injury using multivariate analysis (14). Other studies have not identified any significant association between ACEIs and radiation pneumonitis in individuals affected by lung cancer (17-19).

Studies have also investigated the relationship between ACEIs and radiation-induced nephritis. To date, 10 studies have been conducted between 1986 and 2014 (20-29). Most studies have reported consistent results in the beneficial association between ACEIs and reduced risk of renal toxicity, albeit the majority of these studies (90%) were animal studies. Only 1 study reported that all ACEIs mitigate radiation nephropathy except fosinopril (29). Elsewhere, another study did not report any association between ACEIs and reduced risk of radiation-induced nephritis in a population of lung cancer patients (22).

Moreover, 2 animal studies have demonstrated that ACEIs reduced the prevalence of radiation-induced brain injuries, including cognitive impairment and optic neuropathy (30, 31). Other studies have explored the association between ACEIs and gastrointestinal (GI) toxicity. Six clinical studies conducted between 2004 and 2012 all investigated the effect of hypertension on normal tissue radiation-induced toxicity (32-37). Three of them consistently reported a beneficial effect of the ACEIs on GI tract toxicity (32, 34, 37). One animal study did not find any association between the ACEIs and GI tract toxicity (26).

To date, several studies (animal and human) have investigated the potential association between ACEIs and their protective effects on reducing the incidence of radiation-induced injuries in renal, brain, GI tract, and pelvic cancer. To the best of our knowledge, no study has explored the effect of ACEIs in men with prostate cancer treated by radical radiation therapy with neoadjuvant/adjuvant hormone therapy. We aimed to evaluate whether the concurrent use of ACEIs decreases the incidence, severity, and duration of radiation-induced proctitis in prostate cancer patients treated by radical radiation therapy.

Methods and Materials

The study had Caldecott Institutional Approval (Caldicott/CSAppGN021211). During January 2007 and December 2013, all consecutive patients who underwent radical radiation therapy and neoadjuvant or adjuvant hormone therapy were identified from comprehensive clinical databases hosted at 1 of the main cancer centers in the United Kingdom. Patients were identified from electronic databases through a validated cross-linkage method as described previously by our group (38, 39). Record linkage technique brings together 2 or more records relating to the same individual identified by a common identifier: Community Health Index (CHI) number in this series. Cross-linkage of databases enabled the demographic and clinical data to be securely managed at 1 centralized database for the purpose of this study.

The database with CHI was linked to the following clinical systems:

1. WISDOM oncology system (Web Information System for Data Oncology Management), which securely stores