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Biology Contribution

Mitigation and Treatment of Radiation-Induced Thoracic Injury With a Cyclooxygenase-2 Inhibitor, Celecoxib

Nancy R. Hunter, MS,* David Valdecanas, BS,* Zhongxing Liao, MD,† Luka Milas, MD,* Howard D. Thames, PhD,‡ and Kathy A. Mason, MS*

**Department of Experimental Radiation Oncology, †Division of Radiation Oncology, and ‡Department of Biostatistics, University of Texas MD Anderson Cancer Center, Houston, Texas*

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Summary

The ability of celecoxib to reduce lung toxicity when given to mice after radiation was tested. Significant reduction in time to death was observed when celecoxib was started 80 days after LTI, corresponding to the time at which pneumonitis is expected. This schedule-dependent reduction in lung toxicity suggests that celecoxib could be clinically useful by introduction of reatment months after radiation exposure.

Purpose: To test whether a cyclooxygenase-2 inhibitor (celecoxib) could reduce mortality resulting from radiation-induced pneumonitis.

Methods and Materials: Celecoxib was given to mice twice daily for 40 consecutive days starting on the day of local thoracic irradiation (LTI) or 40 or 80 days later. C3Hf/KamLaw mice were observed for morbidity, and time to death was determined. Results were analyzed using the Cox proportional hazards model.

Results: Timing of celecoxib relative to LTI determined efficacy. A significant reduction in time to death was achieved only when celecoxib was started 80 days after LTI, corresponding to the time when pneumonitis is expressed. For these mice the reduction in mortality was quantified as a hazard ratio for mortality of treated vs untreated of 0.36 (95% confidence interval [CI] 0.24-0.53), thus significantly less than 1.0. Correspondingly, the median lethal dose for treated mice (12.9 Gy; 95% CI 12.55-13.25 Gy) was significantly ($P = .026$) higher than for untreated mice (12.4 Gy; 95% CI 12.2-12.65 Gy).

Conclusions: Celecoxib significantly reduced lung toxicity when administered months after LTI when the deleterious effects of radiation were expressed. The schedule-dependent reduction in fatal pneumonitis suggests that celecoxib could be clinically useful by reintroduction of treatment months after completion of radiation therapy. These findings may be important for designing clinical trials using cyclooxygenase-2 inhibitors to treat radiation-induced lung toxicity as a complement to concurrent radiation therapy of lung cancers. © 2013 Elsevier Inc.

Introduction

Therapeutic agents are needed in radiation therapy to selectively reduce normal tissue injury without diminishing tumoricidal effectiveness and as countermeasures to protect populations from radiologic/nuclear terrorism or accidents (1-4). Agents used to prevent or treat radiation injury are classified as protectors, given before radiation exposure; mitigators, administered during or after radiation exposure but before symptoms of toxicity occur; or treatments, given after the appearance of overt symptoms of radiation injury (1). Only amifostine has been approved as a radioprotector given before or during radiation therapy (3, 4). No drugs are currently approved to mitigate radiation toxicity when given after exposure (4). Agents that are currently in clinical and preclinical development as radiation mitigators have been discussed in recent reviews (3, 4).

Reprint requests to: Kathy A. Mason, MS, University of Texas MD Anderson Cancer Center, Department of Experimental Radiotherapy, 1515 Holcombe Blvd., Houston, TX 77030. Tel: (713) 792-3424; Fax: (713) 794-5369; E-mail: kmason@mdanderson.org

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Cyclooxygenase-2 (COX-2) is an inducible enzyme involved in prostaglandin production in pathologic states such as inflammatory processes occurring in irradiated tissues. In a recent report, meloxicam, an inhibitor of COX-2, administered 1 hour after radiation was shown to increase 30-day survival of whole-body-irradiated mice, though there was no benefit if administration was delayed by 24 hours, and multiple administrations were deleterious (5). Our studies with selective COX-2 inhibitors showed that inhibition of this enzyme slows the growth of established tumors and enhances response to radiation without appreciably affecting radioresponse of normal tissues (6, 7). Subsequent clinical trials used celecoxib concurrently with radiation therapy for the treatment of non-small cell lung cancer (8). An agent that would both sensitize tumors to concurrent radiation and mitigate or treat subsequent normal tissue injury would be an advantageous anticancer therapeutic. Previously, we proposed that selective COX-2 inhibitors might be radioprotective in normal tissues where inflammation significantly participates in the pathogenesis of radiation injury (7). Therefore, we were interested in exploring whether celecoxib given after radiation exposure could be an effective mitigator or treatment for radiation-induced lung damage.

Two syndromes, radiation pneumonitis and fibrosis, which are histologically distinct and separated in time, have been identified in the lung after irradiation. Radiation pneumonitis is an inflammatory reaction that occurs between 80 and 180 days after irradiation in experimental animals (9). This phase is characterized histologically by intra-alveolar and septal edema, infiltration of inflammatory cells, and epithelial and endothelial desquamation. A similar sequence of events is observed in humans (9). Pneumonitis leads to diminished quality of life and may even be lethal in outcome after radiation therapy (10). Symptoms of pneumonitis can be treated with steroids such as prednisone. However, limitations due to adverse affects of clinical steroid therapy and the quest for relatively nontoxic mitigators of radiation injury after accidental exposures or nuclear terrorism have led to investigations of other agents to reduce pneumonitis (10). Preclinical studies have explored the use of agents such as nonsteroidal anti-inflammatory drugs (NSAIDs) (11), lovastatin (12), the angiotensin-converting enzyme (ACE) inhibitor captopril (13), and the antioxidant genistein (14). Our interest is in selective COX-2 inhibitors that exert potent anti-inflammatory activity while causing fewer unwanted side effects (such as ulcerations and bleeding in the gastrointestinal tract) that limit the use of common NSAIDs (7). The present study was designed to determine whether celecoxib would be an effective mitigator or therapeutic agent for radiation-induced pneumonitis.

Methods and Materials

Mice

C3Hf/KamLaw female mice, bred and maintained in our specific-pathogen-free mouse colony, were 3-4 months old at the beginning of experiments. The mice, housed 5 per cage, were exposed to 12-hour light/dark cycles and given free access to sterilized pelleted food (Prolab Animal Diet; Purina, Indianapolis, IN) and sterilized water. The facilities were approved by the Association for Assessment and Accreditation of Laboratory Animal Care and in accordance with current regulations of the US Department of Agriculture and Department of Health and Human Services, and the experimental protocol was approved by and in accordance with guidelines established by the Institutional Animal Care and Use Committee.

Irradiation

Mice were irradiated to the whole thorax (local thoracic irradiation, LTI) using a small animal ^{137}Cs irradiator loaded with 2 opposing sources at a dose rate of 5.5 Gy/min. Radiation was delivered to a tightly collimated 3-cm diameter field, and leakage outside the defined beam was $<1\%$. Mice were restrained (without anesthesia) in Lucite jigs with underarm supports so that only the thorax was centered in the radiation field. Dosimetry showing the heart in the radiation field was similar to that previously described for whole-lung irradiation (15).

COX-2 inhibitor

Celecoxib was obtained from Pharmacia (St. Louis, MO) as a powder and diluted to a concentration of 7 mg/mL in 0.5% methyl cellulose and 0.025% Tween 20 in sterile water. The solution was sonicated 4-5 minutes and kept at room temperature up to 5 days. Celecoxib was administered to mice by gavage at a dose of 25 mg/kg in 0.1 mL twice daily (10-11-hour interval) for a total of 40 days. The dose of celecoxib was based on our previously published results demonstrating its biologic effectiveness as a COX-2 inhibitor in tumor studies (16). When celecoxib and LTI were given on the same day, mice were irradiated 2 hours after the morning gavage.

Assay for lethal radiation-induced pneumonitis

The preclinical model used for studying damage and morbidity (or lethality) from pneumonitis has been reported previously (9, 15). C3H mice are one of the most common models exhibiting pulmonary dysfunction attributed to radiation pneumonitis, and survival is a primary endpoint for assessment of radioprotective and mitigating therapies (2, 9). Mice in the initial study to determine scheduling for celecoxib were irradiated with 13.5 Gy. This dose was based on prior work indicating it to be near the expected radiation dose causing 90% lethality at 180 days after LTI for this strain of mice (9). Further studies included a full range of single doses from 11.00-14.75 Gy. Groups consisted of 10-20 mice each.

Mice were observed daily for signs of morbidity (hunched posture, progressive weight loss, labored breathing). Moribund mice were killed by CO_2 inhalation, and deaths were recorded as they occurred. Median time to death in days and percentage of mice dying at a given dose of radiation within each treatment group were obtained. Deaths were considered a result of pulmonary damage with the caveat that pneumonitis was not histologically confirmed, and in addition, other tissues (esophagus, spinal cord, and heart) may have contributed to morbidity after whole-thoracic irradiation. However, death from pneumonitis occurs at lower radiation doses than death from damage in those tissues (9), though the contribution of multiorgan damage cannot be excluded.

Statistical methods

The primary analysis was realized with the Cox proportional hazards (PH) model, whereby time to death was analyzed in terms

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