CHAPTER 7

Cutaneous and intra-abdominal abscess formation in rats following Radio Frequent Ablation of liver tumors in combination with celecoxib treatment


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Abstract

Background: The present study evaluated the safety of treatment of colorectal liver metastases with Radio Frequency Ablation (RFA) in combination with high doses of the selective cyclooxygenase-2 inhibitor celecoxib.

Materials and Methods: The study was performed in the CC531 rat model for colorectal cancer. Rats were inoculated with CC531 tumor cells subcapsularly in the liver. Rats were randomized for treatment with celecoxib, RFA, or the combination thereof. Celecoxib treatment was started at tumor induction. At three weeks after tumor inoculation liver tumors were treated with RFA and the effects on rat health were monitored.

Results: Treatment that included RFA resulted in significantly (p=0.003) more deaths than sham-operated rats. Treatment that included celecoxib resulted in significantly increased cutaneous wound abscess formation after surgery (p<0.0001). In addition, the combination of celecoxib treatment with RFA resulted in intra-abdominal abscess formation (p<0.0001).

Conclusions: This study indicates that the use of high dose celecoxib in combination with RFA of liver metastases should be treated with caution when applied as anti-cancer treatment modality as additional side effects are induced.
Introduction

Epidemiological studies indicate that the long-term use of aspirin and other Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) reduces the risk of colorectal cancer by 40-50 percent\(^1\). Treatment with cyclooxygenase-2 (COX-2) specific NSAIDs has been shown to reduce polyp size and polyp number in FAP patients with a predisposition to colorectal adenoma and cancer\(^2\). The use of selective inhibitors in combination with additional treatment modalities is being investigated in clinical trials in colorectal cancer patients. Patients with metastases of colorectal cancer confined to the liver can benefit from Radio Frequency Ablation (RFA) if metastases are not surgically resectable\(^3\). Peri-operative treatment with selective COX-2 inhibitors is associated with impaired wound healing and anastomotic failure in animal models \(^4\), but their effects in combination with RFA are unknown.

The aim of this in vivo study was to evaluate the effects and safety of celecoxib treatment in combination with RFA in an animal model. For this we used an in vivo colorectal cancer liver metastases rat model using the syngenic CC531 cell line \(^5\).

Material and methods

In the present study principles of laboratory animal care according to Dutch law were followed. The Animal Welfare Committee of the Leiden University Medical Center approved the study. Forty Wag/Rij rats (Charles River, Zeist, The Netherlands) were inoculated with CC531 tumor cells subcapsularly at two sites in the liver as previously described \(^6\) and randomly assigned to celecoxib treatment, starting at the day of tumor inoculation, or no celecoxib treatment. For celecoxib treatment, celecoxib was mixed into standard chow at a concentration of 1500 mg/kg. In addition, in both groups rats were randomly assigned to treatment with RFA or a sham operation. RFA was performed on one of the two tumors in each rat at 21 days after tumor induction. This resulted in 4 treatment groups: 1, RFA + celecoxib; 2, sham + celecoxib; 3, RFA; 4, sham. RFA was applied using a RITA 1500x RF generator (RITA Medical Systems, Mountainview, CA, USA). A two cm expandable needle was inserted in the right tumor in the upper liver lobe and expanded to 1.5 cm, resulting in a lesion of 1.5 cm in diameter. Power output was set at 90 Watt, temperature was 90° Celsius and when this temperature was reached, an ablation of 2 minutes was performed. The tumor in the left liver lobe remained untreated as a negative control. All rats were operated under semi-sterile conditions. Sham operations were performed as a control. Weight of the rats and general health were monitored thrice weekly and rats were sacrificed on day 40 under general anesthesia. Data were entered into a statistical database (SPSS® version 12-o; SPSS, Chicago, Illinois, USA). Descriptive statistics were used for operative outcomes. The Fisher’s exact test was used to test categorical variables. A P-value of < 0.05 was considered statistically significant.

Results

All rats were operated twice during the study. During the first operation tumors were inoculated subcapsularly in two separate liver lobes. Rats that were randomized for celecoxib treatment
received this drug in chow at a dose of 1500 mg per kg chow, this dose level was the highest used in a study by Reddy et al. and provided optimal inhibition of tumor growth 7. Treatment with RFA or sham operation was performed three weeks after tumor induction. The weights of the rats were followed during the whole study and did not significantly differ among the treatment groups (p=0.76). The clinical outcomes of both operations are summarized in table 1.

<table>
<thead>
<tr>
<th>Event of side effect</th>
<th>Rats per treatment group (No. Of rats showing event/total no. Of rats)</th>
<th>Analysis of event occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1. RFA + celecoxib</td>
<td>2. sham + celecoxib</td>
</tr>
<tr>
<td>post RFA/sham deaths</td>
<td>5/10</td>
<td>0/10</td>
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<tr>
<td></td>
<td></td>
<td></td>
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<tr>
<td>rats developing cutaneous abscesses</td>
<td>10/10</td>
<td>10/10</td>
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<tr>
<td>rats developing intra-abdominal abscesses</td>
<td>10/10</td>
<td>0/10</td>
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</tbody>
</table>

Table 1 Postoperative events registered in rats randomized for liver tumor Radio Frequency Ablation or a sham operation, 3 weeks after induction of liver tumors as described in Material and Methods. Rats had previously been randomized to treatment with celecoxib 1500 mg/kg or no treatment that started immediately after tumor induction. None of the rats had died before RFA or sham treatment. Cutaneous and intra-abdominal abscesses were also present in rats that died following the RFA treatment.

No deaths occurred after tumor inoculation. Eight rats (20%) died after the second operation, of which 5 (12.5%) rats receiving celecoxib. The treatment with RFA resulted in significant more deaths (8 rats, 20%) as compared to sham operation, regardless of celecoxib treatment (0 rats)(p=0.003, Likelihood ratio: 13.1). There were significantly more deaths in the RFA-treated rats in the celecoxib group than in the groups that did not receive celecoxib (p=0.01, Likelihood ratio: 13.95). Rats in the celecoxib group developed intra-abdominal abscesses after RFA treatment (p<0.0001 Likelihood ratio: 17.3)(figure 1a, table 1). Significantly more rats in the celecoxib group compared to the groups that did not receive celecoxib developed cutaneous abscesses after surgery (p<0.0001 Likelihood ratio: 55.5) (figure 2, table 1).
CUTANEOUS AND INTRA-ABDOMINAL ABSCESS FORMATION IN RATS FOLLOWING RADIO FREQUENT ABLATION OF LIVER TUMORS IN COMBINATION WITH CELECOXIB TREATMENT

Discussion

The use of COX-2 inhibitors in the treatment of inflammation and pain has increased in recent years as they are expected to avoid many of the complications associated with regular NSAIDs. Furthermore, they show a potential benefit in prevention and treatment of various malignancies. Clinical studies have employed the use of high dose COX-2 inhibitors in combination with other treatment modalities as COX-2 inhibition could potentially enhance the effectiveness of such treatment, minimize side effects and decrease development of postoperative micrometastases. However, recent studies showed that COX-2 inhibitors affect physiological processes at several levels, causing an increase in cardiovascular complications at high doses and affecting wound and anastomosis healing. In this study treatment with celecoxib was associated with an increase in deaths after RFA treatment. Most notable in this study was the formation of cutaneous abscesses after surgery in all rats receiving celecoxib treatment and additional intra-abdominal abscess formation in rats that received celecoxib treatment in combination with RFA. RFA treatment has been associated with a complication rate of approximately 9%, including hepatic abscess formation. The present study shows that the addition of celecoxib increases the incidence of complications following RFA treatment. Selective COX-2 inhibi-
tors have anti-inflammatory and anti-angiogenic properties. Impairment of neovasculature of the postoperative skin wounds and RFA lesions in combination with the suppression of an adequate immune response against opportunistic infections could be responsible for the side effects as seen in our study.

In summary, this study shows that use of high dose celecoxib in combination with surgery, and especially RFA of tumors, should be treated with great caution due to an increased risk of additional side effects.

**Figure 2** Presence of postoperative cutaneous abscesses in a rat that received celecoxib treatment.
References


