COX-2 inhibitor and irradiation

Saitama Cancer Center
Kunihiko Kobayashi MD, PhD
Synthesis of prostaglandins from arachidonic acid by cyclooxygenase (COX) enzymes
### Difference between COX-1 and COX-2

<table>
<thead>
<tr>
<th></th>
<th>COX-1</th>
<th>COX-2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Structures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(amino acids)</td>
<td>576</td>
<td>604</td>
</tr>
<tr>
<td><strong>Their similarity</strong></td>
<td></td>
<td>61%</td>
</tr>
<tr>
<td><strong>Gene location</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(chromosome)</td>
<td>No. 9</td>
<td>No. 1</td>
</tr>
<tr>
<td><strong>Appearance</strong></td>
<td>permanent</td>
<td>transient</td>
</tr>
<tr>
<td><strong>Site</strong></td>
<td>normal cells</td>
<td>inflammatory cells</td>
</tr>
<tr>
<td></td>
<td></td>
<td>malignant tissue</td>
</tr>
</tbody>
</table>
COX-2 in NSCLC tissue
Prognosis of early stage adenocarcinoma of the lung

Survival distribution

COX-2 negative (n=24)

COX-2 positive (n=57)

P=0.034

Years after operation

T. Hida Clinical Cancer Research Vol. 5, 1001-5, 1999
# COX-2 overexpression in various cancers

<table>
<thead>
<tr>
<th></th>
<th>Colorectal</th>
<th>Gastric</th>
<th>Esophageal</th>
<th>Pancreatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>% with Cox-2</td>
<td>60-100</td>
<td>6-75</td>
<td>78-100</td>
<td>31-90</td>
</tr>
<tr>
<td>overexpression</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Hepatic</th>
<th>Breast</th>
<th>NSCLC</th>
<th>SCLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>% with Cox-2</td>
<td>31-90</td>
<td>29-89</td>
<td>30-95</td>
<td>none</td>
</tr>
<tr>
<td>overexpression</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Prostate</th>
<th>Bladder</th>
<th>Cervical</th>
<th>Head &amp; neck</th>
</tr>
</thead>
<tbody>
<tr>
<td>% with Cox-2</td>
<td>0-87</td>
<td>31-75</td>
<td>28-100</td>
<td>100</td>
</tr>
<tr>
<td>overexpression</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

JNCI 95:1440, 2003
COX-2 and tumorigenesis

COX-2 and tumor angiogenesis

Cox-2 upregulated in cancer cells (HCA-7) leads to PGE1 and E2, which in turn stimulate angiogenic growth factors (VEGF, bFGF, TGF-β, PDGF) and angiogenesis, promoting tumor growth.

References:
COX-2 expression and radiotherapy

○: control, △: SC-'236, ●: irradiation, ▲: SC-'236 + irradiation

PASCO 43:483, 2002
COX-2 expression and radiotherapy

\[ \text{SC-236+ irradiation, } \bullet: \text{irradiation} \]

PASCO 43:483, 2002
COX-2 expression and radiotherapy

< 10% COX-2^+
(75% 5-y overall survival, n = 12)

≥ 10% COX-2^+
(35% 5-y overall survival, n = 12)

COX-2 expression and radiotherapy ④
- Mechanism of radiation potentiation by COX-2 inhibitors-

• Ionizing radiation increases expression of COX-2 and the synthesis of PGs in both normal and tumor cells.

• Induction of apoptosis
  – in the normal tissue, in turn, avoiding necrosis
  – in the tumor tissue

• Inhibition of angiogenesis
  – in the normal tissue, in turn, avoiding inflammation
  – in the tumor tissue
A COX-2 inhibitor
- meloxicam (Mobic®) -
Development of NSAIDs

• The 1st period (1897-1985): Standard NSAID
  – In 1897, aspirin was developed.
  – In 1971, mechanism of NSAID was clarified by Vane.
    ♦ aspirin, indomethacin, diclofenac etc.
• The 2nd period (1986-1993): Prodrug
  – In 1991, COX-1 and COX-2 were found.
    ♦ loxoprofen, etc.
• The 3rd period (1994- ): Selective COX-2 inhibitor
  – In 1994, the COX theory was proposed by Vane.
    ♦ Meloxicam, etodolac, celecoxib etc.
Selective COX-2 inhibitors

meloxicam
etodolac
celecoxib
rofecoxib
nimesulide
NS-398
COX-1 inhibition when blocking COX-2

Antitumor activity of meloxicam

Ratio of colony size of colon carcinoma cells (Moser-S)

Metabolic pathway of meloxicam

* : $^{14}$C

meloxicam

CYP2C9

5'-hydroxymethyl compound

CYP3A4

5'-carboxy compound

Nom-cytochrome pathway

oxamic acid compound

glycoyl compound
Pharmacokinetics of meloxicam

- Single dosing -

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (µg/mL)</td>
<td>0.72±0.20</td>
</tr>
<tr>
<td>T1/2 (hr)</td>
<td>27.6±7.30</td>
</tr>
<tr>
<td>AUC0-168 (µg h/mL)</td>
<td>22.8±3.61</td>
</tr>
</tbody>
</table>

10 mg p.o. dosing

Cmax (µg/mL)     0.72±0.20
T1/2 (hr)         27.6±7.30
AUC0-168 (µg h/mL) 22.8±3.61
Pharmacokinetics of meloxicam
- Multiple dosing -
# Side effects of meloxicam

<table>
<thead>
<tr>
<th></th>
<th>Meloxicam 15mg (n=1590)</th>
<th>Piroxicam 20mg (n=689)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI side effects</td>
<td>1.7%</td>
<td>4.9%*</td>
</tr>
<tr>
<td>Skin reaction</td>
<td>6.2%</td>
<td>4.4%</td>
</tr>
<tr>
<td>AST, ALT ↑</td>
<td>7.4%</td>
<td>6.3%</td>
</tr>
<tr>
<td>BUN, Cr ↑</td>
<td>0.4%</td>
<td>0.9%</td>
</tr>
</tbody>
</table>
A proposed clinical study using Meloxicam (Mobic®)

Daiichi pharmaceutical company in Japan will give us a grant. Meloxicam will be freely given to the patients entered in this clinical trial.
Clinical trials combining celecoxib and radiation therapy

<table>
<thead>
<tr>
<th>Phase</th>
<th>Diagnosis</th>
<th>Treatment</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>NSCLC I/II</td>
<td>Celecoxib+RT</td>
<td>RTOG</td>
</tr>
<tr>
<td>I/II</td>
<td>NSCLC IIB-IIIB</td>
<td>Celecoxib+RT</td>
<td>RTOG</td>
</tr>
<tr>
<td>II</td>
<td>NSCLC III</td>
<td>Celecoxib+CBDCA/TXL/RT</td>
<td>VCC</td>
</tr>
<tr>
<td>II</td>
<td>NSCLC inope I/II</td>
<td>Celecoxib+RT</td>
<td>VCC</td>
</tr>
<tr>
<td>II</td>
<td>NSCLC recurrent</td>
<td>Celecoxib+taxane/RT</td>
<td>VCC</td>
</tr>
<tr>
<td>I</td>
<td>NSCLC inope</td>
<td>Celecoxib dose ↑ + RT</td>
<td>MDACC</td>
</tr>
<tr>
<td>I/II</td>
<td>Esophageal ca.</td>
<td>Celecoxib+CDDP/FU/RT</td>
<td>MDACC</td>
</tr>
<tr>
<td>II</td>
<td>Esophageal ca.</td>
<td>Celecoxib+CDDP/FU/RT</td>
<td>HOG</td>
</tr>
<tr>
<td>II</td>
<td>Cervical ca.</td>
<td>Celecoxib+CDDP/FU/RT</td>
<td>RTOG</td>
</tr>
</tbody>
</table>

JNCI 95:1440, 2003
Possible clinical trials combining meloxicam and radiation therapy

<table>
<thead>
<tr>
<th>Phase</th>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Cervix &amp; head and neck ca.</td>
<td>Meloxicam dose↑+CDDP/RT</td>
</tr>
<tr>
<td>II</td>
<td>Cervical ca. locally advanced</td>
<td>Meloxicam+CDDP/RT</td>
</tr>
<tr>
<td>II</td>
<td>Head and neck ca. locally ad.</td>
<td>Meloxicam+CDDP/RT</td>
</tr>
<tr>
<td>R. II</td>
<td>Cervical ca. locally advanced</td>
<td>Meloxicam+CDDP/RT</td>
</tr>
<tr>
<td>R. II</td>
<td>Head and neck ca. locally ad.</td>
<td>Meloxicam+CDDP/RT</td>
</tr>
<tr>
<td>R. III</td>
<td>Cervical ca. locally advanced</td>
<td>Meloxicam+CDDP/RT</td>
</tr>
<tr>
<td>R. III</td>
<td>Head and neck ca. locally ad.</td>
<td>Meloxicam+CDDP/RT</td>
</tr>
</tbody>
</table>

R.: randomized
A phase I study using Meloxicam (Mobic®)

- Locally advanced cervical cancer or head and neck cancer (n=6 x each dose)
- Meloxicam 15, 20, 25, 30mg/day+CDDP/RT
  - According to phase I study of CDDP/RT for cervical or head & neck cancers, the doses of CDDP and RT will be decided.
- Primary end point: Side effect
- Secondary end point: Response, (Survival time), (QOL)
A phase II study using Meloxicam (Mobic®)

- Locally advanced cervical cancer (n=30-100), or
  Locally advanced head and neck cancer (n=30-100)
- Meloxicam 15mg/day+CDDP/RT
  - According to phase I study of CDDP/RT for cervical or
    head & neck cancers, the doses of CDDP and RT will be
decided.
- Primary end point: Response
- Secondary end point: Survival time, Side effects,
  (QOL)
A randomized phase II study using Meloxicam (Mobic®)

• Locally advanced cervical cancer (n=30-40 x 2), or Locally advanced head and neck cancer (n=30-40x2)
• Meloxicam 15mg/day+CDDP/RT
  – According to phase I study of CDDP/RT for cervical or head & neck cancers, the doses of CDDP and RT will be decided.
• Primary end point: Response, Side effects
• Secondary end point: Survival time, QOL
  – QOL investigation will be easily done by Care Notebook.
A randomized phase III study using Meloxicam (Mobic®)

- Locally advanced cervical cancer (n=100x2), and/or Locally advanced head and neck cancer (n=100x2)
- Meloxicam 15mg/day+CDDP/RT
  - According to phase I study of CDDP/RT for cervical or head & neck cancers, the doses of CDDP and RT will be decided.
- Primary end point: Survival time
- Secondary end point: Response, QOL, Side effects
  - QOL investigation will be easily done by Care Notebook.
Meloxicam, a COX-2 inhibitor, is considered to have both antitumor effects for head/neck cancer and cervical cancer and protective effects for the oral mucosa and the rectal mucosa, respectively, indicating that the aim of clinical studies must focus on both response/survival and side effects/QOL.

Safety for meloxicam at a dose of 15mg/day has been already established. Meloxicam at a dose of 15mg/day reduces inflammatory pain such as RA, indicating that this dose inhibits COX-2. These indicates no need of phase I study.

Single arm phase II study cannot prove the benefit of COX-2 inhibitor at all. This study needs the control arm.

Randomized phase III study is the best, but this needs a lot of patients.
## Which trial do you recommend? ②

<table>
<thead>
<tr>
<th>Phase</th>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Cervix &amp; head and neck ca.</td>
<td>Meloxicam dose↑+CDDP/RT</td>
</tr>
<tr>
<td>II</td>
<td>Cervical ca. locally advanced</td>
<td>Meloxicam+CDDP/RT</td>
</tr>
<tr>
<td>II</td>
<td>Head and neck ca. locally ad.</td>
<td>Meloxicam+CDDP/RT</td>
</tr>
<tr>
<td></td>
<td>R. II Cervical ca. locally advanced</td>
<td>Meloxicam+CDDP/RT</td>
</tr>
<tr>
<td>✓</td>
<td>R. II Head and neck ca. locally ad.</td>
<td>Meloxicam+CDDP/RT</td>
</tr>
<tr>
<td>✓</td>
<td>R. III Cervical ca. locally advanced</td>
<td>Meloxicam+CDDP/RT</td>
</tr>
<tr>
<td></td>
<td>R. III Head and neck ca. locally ad.</td>
<td>Meloxicam+CDDP/RT</td>
</tr>
</tbody>
</table>

R.:randomized
A randomized phase II study using Meloxicam (Mobic®)

• This study will be an optional study in our group.

• The protocol using patients with cervical cancer will be proposed.
A randomized phase II study using Meloxicam (Mobic®) – draft -
A randomized phase II study - Aim

Determine the efficacy of meloxicam on concurrent chemoradiotherapy using cisplatin in patients with locally advanced cervical cancer

Primary endpoint:  Response
   Side effects

Secondary endpoint:  Survival time
   QOL
A randomized phase II study - Entry criteria

1. Squamous cell carcinoma of the uterine cervix
2. Stage IIB (≥ 4 cm in diameter) and IIB disease (FIGO 1994)
3. Age; 20-70 years
4. PS; WHO 0-2
5. No prior chemotherapy, radiotherapy, and surgery to the pelvis
6. Life expectancy; longer than 6 months
7. Measurable disease
8. Adequate bone marrow, hepatic, and renal functions:
   - WBC ≥ 3000/mm³
   - Hb ≥ 10g/dl
   - Platelet ≥ 100,000/mm³
   - Total bilirubin ≤ 1.5mg/dl
   - AST/ALT ≤ 2 times upper limit of normal
   - Serum creatinine ≤ 1.5mg/dl
9. Written informed consent
A randomized phase II study - Exclusion criteria

1. Severe concomitant illness
2. History of other malignancies within the past 5 years except basal cell carcinoma or squamous cell carcinoma in-situ of the skin
3. Tumor with infiltration of lower 1/3 of the vagina
4. Patients who are pregnant or lactating
5. Patients planned for surgery following radiotherapy
A randomized phase II study - Entry & randomize

Ensure to meet the entry criteria, informed consent

↓

Entry

↓

randomize (block randomization: institution)

↓

Arm 1: ChemoRT with meloxicam

Arm 2: without it
A randomized phase II study – Treatment ①

<table>
<thead>
<tr>
<th>Arm 1: ChemoRT with meloxicam</th>
<th>Arm 2: without it</th>
</tr>
</thead>
<tbody>
<tr>
<td>meloxicam p.o.</td>
<td>none</td>
</tr>
<tr>
<td>For 8 weeks (from day –1 to day 56),</td>
<td>(Prophylactic use of NSAID is prohibited.)</td>
</tr>
<tr>
<td>15 mg/body/day p.o. 1 x m</td>
<td>↓</td>
</tr>
<tr>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>&lt; weekly CDDP and concurrent irradiation &gt;</td>
<td></td>
</tr>
</tbody>
</table>

CDDP 40mg/m2/weekly x 5 with hydration of 2000mL.
Concurrent RT
A randomized phase II study – Treatment ②

Weeks

1  2  3  4  5  6  7  8

External beam radiotherapy

Intracavitary brachytherapy (HDR)
(LDR)

Cisplatin

Arm A: With meloxicam
Arm B: Without meloxicam
A randomized phase II study – Treatment

- **External beam radiotherapy**
  Fractionation schedule: 1.8 - 2.0 Gy/fraction, 5 fractions/week
  Total dose: approximately 50 Gy
  Whole pelvis 30-40 Gy, Central shielding 20-10 Gy
  10-15 Gy of boost irradiation to the bulky parametrial disease or gross lymph node metastases is allowed.

- **Intracavitary brachytherapy**
  HDR treatment: 24-28 Gy / 4 fractions (6-7 Gy/fraction)
  LDR treatment: 30-40 Gy / 1-2 fractions

- **Chemotherapy**
  - Cisplatin 40 mg/m² d.i.v. weekly, week 1-week 5

- **COX-2 inhibitor**
  - With meloxicam: For 8 weeks (from day -1 to day 56), 15 mg/day p.o. 1x m
  - Without meloxicam: Prophylactic use of NSAID or COX-2 inhibitor is prohibited
A randomized phase II study – Treatment ③

In case of

- S-Cr $\geq 2.0$ mg/dl $\Rightarrow$ Withhold CDDP
- WBC $< 3,000$ /mm$^3$ $\Rightarrow$ Withhold CDDP
- Pl $< 75,000$ /mm$^3$ $\Rightarrow$ Withhold CDDP
- Gastric ulcer $\Rightarrow$ Withhold meloxicam
- Grade $\geq 3$ nonhematological toxicities $\Rightarrow$ Withhold CDDP+RT
- Grade 4 hematological toxicities $\Rightarrow$ Withhold CDDP+RT
- PSR 3 or 4 $\Rightarrow$ Withhold CDDP+RT
A randomized phase II study - Evaluation

- Plain pelvic MR or enhanced CT scan before the treatment, and after completion of RT
  - Response
- Evaluation of acute toxicities by NCI CTC up to 90 days from the beginning of the treatment and late toxicities
  - Side effects
- QOL evaluation before the treatment, at the end of RT, 1 year and 2 years after the treatment
  - QOL
- Follow up at least for 2 years
  - Survival
A randomized phase II study - Evaluation

Plain pelvic MR or enhanced CT scan

- Before the treatment and at the end of the treatment
- The same test (CT/MR) before and after the treatment should be performed.
- For two times of testing, about 400 US dollars per person will be given to the institution joined the study except for Japanese institutions from the grunt.

- Please discuss about this matter.
  - We consider that only single type (MR) of scan should be employed --- .
A randomized phase II study - Evaluation

QOL evaluation

- before the treatment, at the end of RT, 1 year and 2 years after the treatment
- Using a validated QOL questionnaire, Care Notebook
- Paying some money to the patient when answering Care Notebook, to avoid low return rate of the questionnaire
A randomized phase II study -Cost

- Meloxicam 15mg x 56 days
  - About 100 US dollars (but no cost in control)
- Two times of plain pelvic MR for response
  - About 400 US dollars
- Evaluation of acute and late side effects
  - No cost
- Four times of QOL evaluation
  - 5 US dollars x 4 times = 20 US dollars
- Follow up at least for 2 years
  - No cost

✧ 500 US dollars per person will be given to the institution joined the study except for Japanese institutions from the grunt.
✧ Minimum number of patients is 4 in one institution joined the study.