Inflammation in mRCC: Target or Prognostic Factor?

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SIGNS OF INFLAMMATION

BIOCHEMICAL SIGNS

C-reactive protein

Erythrocyte sedimentation rate
**SIGNS OF INFLAMMATION**

**BIOCHEMICAL SIGNS**
- C-reactive protein
- Erythrocyte sedimentation rate

**Indirect signs**
- Trombocytosis
- Anemia
- Neutrophilia

**CLINICAL SIGNS**
- Fever
- Anorexia
- Weight loss

**ON PATHOLOGY**
- Tumor infiltration by immunitary cells

**NOT ROUTINELY ASSESSED CYTOKINES**
- IL6
- IL8
An elevated CRP predicts poor survival in patients with localized RCC (1)(2)(3).

On 313 patients (CRP in mg/l):
RCC specific mortality

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### BASELINE CRP LEVELS IN THE METASTATIC SETTING (IMMUNOTHERAPY)

<table>
<thead>
<tr>
<th>n</th>
<th>Therapy</th>
<th>CRP</th>
<th>Impact</th>
<th>Source(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>425</td>
<td>Cytokines</td>
<td>≥ 11 mg/l</td>
<td>Worse OS</td>
<td>(1)</td>
</tr>
<tr>
<td>110</td>
<td>IL-2</td>
<td>&gt; 8 mg/l</td>
<td>Most independent prognostic factor</td>
<td>(2)</td>
</tr>
<tr>
<td>181</td>
<td>Nephrectomy and medical treatment or medical treatment only, in most cases immunotherapy</td>
<td>&gt; 67 mg/l</td>
<td>Remarkably poor prognosis despite treatment =&gt; QUID role of serum CRP in the decision whether to perform nephrectomy at the onset?</td>
<td>(3)</td>
</tr>
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### BASELINE CRP LEVELS IN THE METASTATIC SETTING (ANTI-VEGFR-TKIs)

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<th>CRP</th>
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<tr>
<td>41</td>
<td>Sunitinib</td>
<td>&gt; 3 mg/l</td>
<td>Shorter PFS (6.0 vs 19.0 months; p=0.036) Independent prognostic marker of OR (p=0.0163)</td>
<td>(1)</td>
</tr>
<tr>
<td>45</td>
<td>Sorafenib (after relapse on cytokines)</td>
<td>Elevated</td>
<td>A significantly poorer RR (p=0.031) In patients with normal baseline CRP levels: Hazard ratio for PFS was 2.24 (95%CI 1.01-5.00; p=0.046)</td>
<td>(2)</td>
</tr>
<tr>
<td>52</td>
<td>Sunitinib or sorafenib</td>
<td>&gt; 8 mg/l</td>
<td>OS 15.9 months vs not reached (p=0.003)</td>
<td>(3)</td>
</tr>
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</table>

In 187 RCC patients treated with **sunitinib**

Beuselinck B et al. Manuscript in preparation
IL6

- mRCC: frequently associated with elevated IL6 levels
  - In vitro: some renal tumors can produce IL6.

- Higher IL6-levels
  - In patients with metastases compared to patients with tumors confined to the kidney.
  - Correlate with metastatic progression, poor prognosis, shorter survival post-nephrectomy.
  - Correlate with poor response to IL2 therapy.
  - In poorly differentiated tumors

- IL6 leads to production of CRP in the liver through the gp130 receptor

IL8 (Neutrophil chemotactic factor)

1. Pro-inflammatory: induces chemotaxis in target cells (neutrophils and other granulocytes) causing them to migrate toward the site of infection.

2. A potent promoter of angiogenesis.

IL1

Tumor necrosis factor alpha
**IL8 (Neutrophil chemotactic factor)**

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**IL1**

*Tumor necrosis factor alpha*

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**VEGF**

- Important overexpression in RCC
- Leading to angiogenesis
- Chemotactic for macrophages and granulocytes and important for vascular permeability
PROGNOSTIC VALUE OF BASELINE VEGF-LEVELS IN THE METASTATIC SETTING

In 348 placebo-treated patients in the TARGET-trial:

Higher serum baseline VEGF levels linked to poorer OS.

Increased baseline serum VEGF associated with decreased survival in sunitinib-treated patients:

— VEGF-levels >707 pg/ml versus <707 pg/ml: median survival of 4.37 versus 11.2 months

— Patients with higher baseline VEGF levels: higher probability of disease progression

PROGNOSTIC VALUE OF BASELINE VEGF-LEVELS IN THE METASTATIC SETTING

- Placebo group: high baseline serum VEGF patients: shorter PFS than patients with low baseline VEGF.
- Reflecting an aggressive tumor.
- Thus indicating that high baseline VEGF-levels have a negative prognostic value.

PROGNOSTIC VALUE OF BASELINE VEGF-LEVELS IN THE METASTATIC SETTING

In **pazopanib** pivotal trial (versus **placebo**):

Higher serum VEGF levels: negative prognostic markers for OS in both treatment groups:

- In **pazopanib** treated patients: High VEGF-levels: 20.0 versus 25.5 months (p=0.04)
- In **placebo** treated patients: High VEGF-levels: 6.1 versus 23.5 months (p=0.001)

In the **pazopanib** pivotal trial: higher baseline IL6 levels: a negative prognostic markers for PFS and OS:

- In 118 placebo-treated patients: PFS 9.9 versus 24.0 weeks (p<0.0001).
- In 118 placebo-treated patients: OS 8.4 versus 28.0 months (p<0.0001).
- In 225 pazopanib-treated patients: OS 19.0 versus 29.0 months (p<0.0001).

PROGNOSTIC VALUE OF BASELINE IL8-LEVELS IN THE METASTATIC SETTING

Polymorphisms in IL8 linked with higher IL8 expression => more alternative non-VEGF-dependent angiogenesis

PFS curves for IL8 2767A>T rs1126647
T-allele is linked to increased IL8 levels

PFS curves for IL8 -251T>A rs4073
A-allele is linked to increased IL8 levels

Polymorphisms in IL8 linked with higher IL8 expression => more non-VEGF-dependent alternative angiogenesis

WHY IS INFLAMMATION ASSOCIATED WITH POOR OUTCOME?

1. INFLAMMATION: a consequence of a more extended and more aggressive disease?
   - Tumor cells secreting pro-inflammatory cytokines?
   - Tumor causing an inflammatory reaction in the tumor micro-environment?

2. INFLAMMATION: a driver of the disease?
   - Stimulating tumor growth?
   - Promoting invasion (destruction of basal membrane)?
   - Infiltrating immune cells promote carcinoma progression into metastatic disease
   - Can induce EMT, which provides tumors with invasive, migratory and stem cell properties

3. INFLAMMATION: an inflammatory state leading to decreased treatment tolerance?

… ASSOCIATED WITH GOOD OUTCOME?

4. INFLAMMATION: a sign of an immune reaction against the tumor?
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Kidney Cancer Symposium
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TARGETING INFLAMMATION BY TARGETING TNF INFLIXIMAB = ANTI-TNF-MAB

2 sequential phase II studies of infliximab in immunotherapy-resistant or refractory RCC (1)

- Study 1: 16% (3/19) PR. Median duration of response 7.7 months
- Study 2: 61% (11/18) SD. Median duration of response 6.2 months
- Higher TNF-alpha levels => poor survival

Phase I/II trial of sorafenib and infliximab in advanced RCC (2)

- mPFS 6 months
- mOS 14 months
- The combination of sorafenib and infliximab does not warrant further evaluation in advanced RCC

**Siltuximab (CNTO 328)**

- Chimeric murine-human monoclonal antibody that binds with high affinity and specificity to IL6
- Preclinical experience has shown that siltuximab inhibits the growth of human RCC tumors in nude mice

**PHASE I/II STUDY**

- Siltuximab continuous dosing in 68 mRCC patients
- Dosis ranging 1 mg/kg to 6 mg/kg

TARGETING INFLAMMATION

— The PR patient had neck and pancreatic metastases that had progressed despite HD IL2, IFN-alpha and 5-FU.

— He was progressive on day 283.

— CRP levels decreased from baseline 36 mg/l to below 10 mg/l and remained suppressed throughout the therapy.

COLON CARCINOMA

— Colon carcinoma cells rendered deficient in HIF transcription factors
— IL8: dominant role in the generation and maintenance of the tumour microcirculation
— Tumour angiogenesis blocked with a neutralising anti-IL8 antibody (1)

RENAL CELL CARCINOMA

— IL8-mediated angiogenesis: a key compensatory mechanism of resistance to sunitinib in murine models
— IL8 expression has been observed to be elevated in RCC tumors from patients refractory to sunitinib treatment
— Anti-IL8 antibody did not affect tumor growth in xenograft-bearing animals not yet exposed to a VEGF TKI, but after development of resistance to sunitinib, the combination of sunitinib and an anti-IL8 antibody effectively reduced tumor growth (2).

TARGETING INFLAMMATION BY TARGETING PGE2

CYCLOXYGENASE-2 (COX-2):
- Involved in prostaglandin E2 synthesis
- Associated with higher renal cell carcinoma stage
- COX-2 inhibition enhances IFN-α anti-tumor immune effects in pre-clinical models

PHASE II TRIAL: CELECOXIB AND IFN-A IN MRCC PATIENTS WITH MAXIMAL COX-2 EXPRESSION
- 17 cytokine-naive mRCC patients with tumors expressing ≥10% maximal COX-2 staining by IHC
- IFN-α 5 million units daily and celecoxib 400 mg orally twice daily

RESULTS
- 3 PR: objective response rate 18%
- TTP 5.6 months

=> Celecoxib plus IFN-α in RCC patients with maximally staining COX-2 tumors does not significantly enhance overall RR over IFN monotherapy.

In 83 patients with clear cell mRCC treated with sorafenib (after cytokines)

Serum ESR tested before treatment and Q4W after first administration of sorafenib.
— Baseline ESR levels ranged from 3 to 154 mm/h
— 43 (41.0%) patients had an ESR level higher than 40 mm/h.
— Median PFS was 10.0 months (95% CI 7.6-12.4 months).

Independent predictors for PFS in multivariable Cox regression model analysis:
— Performance status
— Time from diagnoses to sorafenib treatment
— Number of metastatic organs
— ESR kinetics

ESR kinetics can be useful to monitor the treatment response and to predict PFS for mRCC patients treated with sorafenib as second-line therapy.

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<th>mPFS</th>
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<tr>
<td>Decreased ESR</td>
<td>27 months</td>
</tr>
<tr>
<td>Stable ESR</td>
<td>12 months</td>
</tr>
<tr>
<td>Increased ESR</td>
<td>6 months</td>
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The most efficient anti-inflammatory therapy is most probably anti-VEGF-therapy!
Targeting an “UPSTREAM”-target, not a collateral event

Inflammation in mRCC: Target or Prognostic Factor?

=> RATHER A PROGNOSTIC FACTOR

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