Results of the CONKO* 004 trial

A prospective, randomized trial of chemotherapy with or without the low molecular weight heparin enoxaparin in patients with advanced pancreatic cancer


Universitätsmedizin Berlin - Charité, Berlin; Hospital, Hagen; Hospital St. Elisabeth & St. Barbara, Halle; Outpatient Department, Kronach; Sana Hospital, Berlin-Lichtenberg; Outpatient Department, Jena. Germany

Supported by: Sanofi Aventis Deutschland GmbH, Lilly Deutschland, AIO, CAO, Deutsche Krebsgesellschaft e.V.

*CHARITÉ ONKOLOGIE
Disclosure

Consultant or Advisory Roles for:

Amgen, GSK, Lilly, Merck,
Pfizer, Roche, Sanofi-Aventis

Research Grants from:

Amgen, Lilly, Sanofi-Aventis
**CONKO-004 Rationale**

High risk of venous thromboembolic events (VTE) in pts with advanced pancreatic cancer (APC).

Chemotherapy increases the risk of VTE.

VTE causes morbidity, mortality, resource utilisation.

LMWH are effective anticoagulants to prevent VTE.

Trials of primary prophylaxis of VTE with LMWHs in non-surgical pts. are non-conclusive - A matter of LMWH dose?

Primary endpoint

Symptomatic VTE is a negative prognostic indicator of survival with 1-year OS in APC-pts of 12% vs 36% in those w/o VTE.

LMWH is discussed to improve OS in cancer.

A retrospective study and a small-sized trial in APC pts suggest favourable effects of LMWH on RR and OS.

**Blom JW et al 2006, Chew et al. 2006**

**Otten HM et al. 2004**

**Geerts WH et al. 2008**

**Geerts WH et al. 2008**

**Sorensen HT et al. 2000**

**Lazo-Langner A et al. 2007**

**Von Delius et al. 2007, Icli F et al. 2007**
**CONKO-004** Endpoints

**Primary Endpoint**
- Symptomatic clinically relevant VTE (DVT of the leg or pelvis or upper extremity, PE) within the first 3 months of chemotherapy

**Secondary Endpoints**
- VTE within the first 6, 9 and 12 months
- **Major bleeding within the first 3, 6, 9, and 12 months**
- PFS, OS, RR
- Toxicity
**CONKO-004 Study Design**

**Randomization**

- **Chemotherapy**
- **Chemotherapy + enoxaparin**

**Chemotherapy + enoxaparin**

- **E 1mg/kg/d**
- **Primary endpoint**
- **E 40mg/d until PD**

**Treatment for 3 months:** VTE, Bleeding, RR, PFS, OS

**Response evaluation at least every 12 weeks:** VTE, Bleeding, RR, PFS, OS
Gemcitabine was „standard“ since several years

Favourable results in randomized phase II/III trials in patients with good PS

- with Gem/CDDP or Gem/5-FU/FA and Gem/Cap

Gem/CDDP/5-FU and Gem/FA/5FU/CDDP with remarkable RR and 1-year OS

References:

3. Heinemann et al.; BMC Cancer 2008;8:82-93
6. Oettle et al. unpublished
Gemcitabine was „standard“ since several years

Favourable results in randomized phase II/III in patients with good PS
  • with Gem/CDDP or Gem/FA/5-FU and Gem/Cap

Gem/CDDP/5-FU and Gem/FA/5FU/CDDP with remarkable RR and 1-year OS

**Patient allocation according to Karnofsky-PS (KPS) and plasma creatinine level**

KPS > 80 % + creatinine < ULN

- Gemcitabine (1000 mg/m²)
- Folinic acid (200 mg/m²)
- FU (750 mg/m² 24 h CI)
- CDDP (30 mg/m²)
  - d1, 8; 22

KPS 60-70 % or creatinine > ULN

- Gemcitabine (1000 mg/m²)
  - d1, 8, 15; 29

H. Riess
CONKO-004 Study design

Primary endpoint (3 months)

Patient allocation
KPS 60-70% or creatinine > ULN
GEM
R
GEM +
Enoxaparin
GEM +
E
GEM

KPS ≥ 80% + creatinine ≤ ULN
GFFC
R
GFFC +
Enoxaparin
GFFC
GEM

Enoxaparin 1mg/kg/d
E 40mg/d
CONKO-004 Entry Criteria

- Histologically proven advanced pancreatic carcinoma
- Measurable disease
- No prior chemotherapy
- Karnofsky performance status ≥ 60% (out-patients)
- No active infection
- Adequate hematologic, and hepatic function
- Calculated creatinine clearance > 30 ml/min
- No major hemorrhage (2 weeks), ASA (>500mg)
- No VTE within the previous 2 years
- No indication for anticoagulation
- Written informed consent
Hypothesis:
Significant decrease in the incidence of symptomatic VTE due to prophylactic use of enoxaparin (from expected 10% to 3%)

Sample size:
540 patients (1:1 ratio), including 15% drop-out rate or 24 pts with VTE

Strata:
KPS (60-70% / 80-100%), stage (M0 / M1), primary disease / relapsed disease, creatinine level (≤ / > ULN)

H. Riess
According to protocol recruitment was stopped in January 2009 after 24 pts with VTE had been reported.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Observation (n=152)</th>
<th>Enoxaparin (n=160)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median, [range])</td>
<td>63 [27-83]</td>
<td>62 [32-81]</td>
</tr>
<tr>
<td>Sex (male / female)</td>
<td>62 / 38</td>
<td>57 / 43</td>
</tr>
<tr>
<td>Stage (M1 / M0)</td>
<td>75 / 25</td>
<td>74 / 26</td>
</tr>
<tr>
<td>Primary / Relaps</td>
<td>87 / 13</td>
<td>84 / 16</td>
</tr>
<tr>
<td>KPS (60-70 / 80-100)</td>
<td>15 / 85</td>
<td>16 / 84</td>
</tr>
<tr>
<td>Creatinin (≤ / &gt; ULN)</td>
<td>95 / 5</td>
<td>96 / 4</td>
</tr>
</tbody>
</table>
Patient Allocation

01/09 (33 centers)

Patient allocation \( n = 312 \)

Primary endpoint (3 months)

- **GEM +**
  - 27 pts
  - KPS 60-70% or creatinine > ULN

- **GEM**
  - 57 pts
  - KPS 80-70% or creatinine > ULN

- **GEM + E**
  - GFFC 125 pts
  - KPS > 80% + creatinine < ULN
  - GFFC + enoxaparin 130 pts

- **GEM**
  - enoxaparin 30 pts

- **GEM**
  - GFFC 125 pts

Date of Analysis: April 2009

H. Riess
Venous thromboembolic events
(one pt. with symptomatic proximal DVT and PE)

<table>
<thead>
<tr>
<th>Event</th>
<th>Observation</th>
<th>Enoxaparin</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary embolism</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Proximal leg DVT</td>
<td>9</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Distal leg DVT only</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Upper extremity DVT</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>All (VTE)</td>
<td>16</td>
<td>2</td>
<td>18</td>
</tr>
<tr>
<td>All (pts)</td>
<td>15</td>
<td>2</td>
<td>17</td>
</tr>
</tbody>
</table>

Secured by an independant EPC
**CONKO-004**  
**VTE - first 3 months (ITT)**

- VTE rate: **9.9 % vs. 1.3 %**  
- p < 0.01  
- aRR 8.6 %  
- RRR 87 %  
- NNT 12  

---

H. Riess
Relative VTE rates according to chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>aRR %</th>
<th>RRR %</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEM</td>
<td>12.4</td>
<td>79</td>
<td>0.3</td>
</tr>
<tr>
<td>GFFC</td>
<td>6.6</td>
<td>90</td>
<td>0.025</td>
</tr>
</tbody>
</table>

Observation Enoxaparin

Gem

GFFC
CONKO-004  Bleeding - first 3 months (ITT)

Observation  Enoxaparin
2.63 %  vs.  3.75 % (rate of major bleeding)

Overall: 9 non-fatal and 1 fatal * upper gastrointestinal hemorrhages

H. Riess

Secured by an independent EPC
## CONKO-004 VTE, Bleeding

<table>
<thead>
<tr>
<th></th>
<th>Median follow-up 30.4 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VTE</strong></td>
<td>E 8 (5.0 %) Δ 10.5 % p &lt; 0.05</td>
</tr>
<tr>
<td></td>
<td>O 22 (15.5 %)</td>
</tr>
<tr>
<td><strong>Bleeding</strong></td>
<td>E 10* (6.3 %) Δ 3.3 % p = 0.6</td>
</tr>
<tr>
<td></td>
<td>O 15*# (9.9 %)</td>
</tr>
</tbody>
</table>

Three letal bleedings (**#)

* 1 tumor-associated letal GI - bleeding, both in GFFC-treated pts. (12.4, 13.4 w)
# 1 letal oesophageal hemorrhage in a Gem-treated pt. (16.7 w)
After a median follow up of 30.4 weeks

A very preliminary estimation of overall survival resulted in – still? – comparable
29 weeks for Observation (mOS)
and
31 weeks for Enoxaparin (mOS)
Patients with advanced pancreatic cancer do have a high risk of symptomatic and clinically relevant VTE, when undergoing first-line chemotherapy.

Performance status may be more important than intensity of chemotherapy.

The LMWH enoxaparin (1mg/kg bw/d) significantly – and clinically relevant - reduces the rate of symptomatic thromboembolic events.

Enoxaparin given in a half-therapeutic dose can be applied safely on an out-patient basis.

The effects of enoxaparin on RR, PFS, and OS will be analysed after an adequate follow-up time.
CONKO-004  Thanks to ...

- Patients and their families for participating

- Investigators in the different centers