Medical Management of Pancreatic Cancer

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Klinische Kooperationseinheit für Molekulare Gastroenterologie
Topics

- Best supportive Care
- Palliative Chemotherapy
- Novel developments
  - Targeted Therapy
  - Gene Therapy
Best Supportive Care

• BSC
  – Nutrition
  – Pain
  – Psychological Support

  – Special aspects
    • Jaundice
    • GI obstruction
Anorexia/Weight loss

- Patients w/ PDAC have a special wasting
  - Caloric demand
    - ↑ at rest
    - ↓ in total

- Serum CRP correlates with
  - Weight
  - Food intake
  - survival

Pain
Anxiety
Sorrow

loss of appetite

GI-Problems

metabolic factors

Wigmore et al., BJC 1997; Moses et al., BJC 1997
Treatment

- Nutritional advice and supervision
  - Enteral formula feeding
- Supplements
  - Pancreatic enzymes
  - EPA
  - Cannabinoids (THC)
  - Thalidomide

Wigmore et al., Nutr. Cancer 2000; Burns et al., Cancer 2004; Walsh et al., Supp Care Cancer 2003; Gordon et al., Gut 2005
Pain

- WHO scheme
- THC is more accepted
- Some substances may have additional aspects
  - Cox2-Inhibitors
  - Cannabinoids

Radbruch & Elsner, Der Internist 2005, in press
COX-2 inhibitor

- Celecoxib 400 mg bid + 5-FU
  - 2nd line Tx
  - Intention-to-treat
- Phase I study
- 17 patients
- 2 PR, 2 SD = RR 12% (0-27)
- Median survival 15 wks

Milella et al., Cancer 2004, 101: 133-138
Cannabis

- Inhibition of DNA-synthesis
- Inhibition of VEGF-pathway

Blázquez et al., Cancer Research 2004, 64: 5617-5623
Psycho-Oncology

- Special attention in pancreatic cancer
  - Symptoms such as
    - Anxiety
    - Depression
    - Panic
  may precede diagnosis of pancreatic cancer
Epidemiology of PDAC

- Incidence
  - #10 (#9) of solid tumors

- Cancer related deaths
  - #4

Jemal et al., CA Cancer Statistics 2005, 55: 10-22
Epidemiology of PDAC

- Incidence of pancreatic cancer remains stable

Jemal et al., CA Cancer Statistics 2005, 55: 10-22
Epidemiology of Cancer

• Cancer outscores heart disease in patients „younger“ than 85 years

Jemal et al., CA Cancer Statistics 2005, 55: 10-22
Epidemiology of PDAC

- Pancreatic cancer is diagnosed at advanced stages

Jemal et al., CA Cancer Statistics 2005, 55: 10-22
Geography

- Incidence: 8/100,000/y
- Age peak 60-70 LJ
- Wide variation within Europe
  - Reasons unknown
Clinical situation with PDAC

- Late Diagnosis
  - 20% operable
  - 80% inoperable & metastasized

- Resistant to
  - Chemotherapy
  - Radiation therapy

- Survival time
  - Median ≈ 5-6 months (Stage III & IV)
  - 1 year survival ≈ 10%
  - 5 year survival ≈ 5%

- Incidence = Prevalence
Current Situation

- pre-OP
- Diagnosis
- neo-adjuvant
  - R0 Resection
    - adjuvant
      - 10 - 36 %
    - „cure“
  - intra-operative
    - 5 - 22 %
- Palliative Therapy
- Median survival: < 1 y (5-6 m)
- 5 year survival: < 5 %
Clinical benefit
Gem 23.8 %
5-FU 4.5 %
„Fixed-dose“ Gemcitabine

- Phase II RCT
- 92 Patienten
- Gemcitabine 1.500 mg/m² über 150 min. vs. 2.200 mg/m² über 30 min.
- Vorteile für FDR

Tempero et al., JCO 2003, 21:3402
GEM + 5-FU/FA

• Phase III RCT
• 473 patients
• No difference in survival

Riess et al., ASCO 2005 #4009
GEM + Capecitabine/Oxaliplatin

- Phase II RCT
- 190 patients/44 centers
- Capecitabine + Oxaliplatin vs. Capecitabine + Gemcitabine vs. Gemcitabine + Oxaliplatin
- To date, NO regimen superior

Heinemann et al., ASCO 2005 #4030
Gemcitabine + Capecitabine

- Phase III RCT
- 319 patients/33 centers
- GEM + Cap Vs. GEM
- NO difference

Herrmann et al. (SAKK+CECOG), ASCO 2005 #4010
EORTC-GI 40984

Number of patients at risk:

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Lutz et al. (EORTC), JCO 2005, in press
Second line therapy

- Phase III RCT
- 2nd line after GEM
- OFF
  - FU 2g/m² (24h)
  - FA 200 mg/m² (30 min) d1, d8, d15, d22
  - OXA 85 mg/m² (2h)
- versus BSC

- 46 pt interim analysis
- mOS 21 wk vs. 10 wk (p = 0.007)
- OS 40 wk vs. 34 wk (p = 0.03)
- Control arm closed

Oettle et al., ASCO 2005 #4031
Problem with PDAC

• „from the analysts couch“*
  – Few cytotoxic drugs work convincingly
    • ≥ 30% difference
    • VERY few work in pancreatic cancer

*: Atkins & Gershell, Nat Rev Cancer 2002, 1: 845
Pancreatic Cancer Pathways

Receptor-Tyrosine-Kinase (RTK)

Cell membrane

SMAD2/3 SMAD3

Ras

SMAD4

ERK1/2 ERK1/2-P

MEK MEK-P

RAF RAF-P

FOS Jun/AP1 p21 p27 cyclin E PCNA

PCNA

FOS Jun/AP1 p21 p27 cyclin E

Target for therapy = targeted therapy
PDAC: beyond the tumor cell

- Tumor cells embedded in dense stroma (= desmoplasia)
  - Epithelial tumor cells
  - Stroma
    - Extracellular matrix
    - Stellate cells
    - Vascular endothelial cells

- Expression of growth factors ...
  - EGF
  - FGF
  - VEGF
  - PDGF

  ... their receptors ...
  - EGF-R
  - PDGF-R

  ... and matrix proteins and enzymes ...
  - Matrix-metalloproteinases

... as targets for therapy
Targeted Therapy

- Several compounds are registered
- NONE cleared for pancreatic carcinoma
- Phase II & III studies up and running
  - Stage III&IV inoperable
Cetuximab ($\alpha$-EGF-R)

- Phase II trial
- 61 pt. 58 $\geq$ 1+ pos, 41 in trial
- 5/41 (12%) PR
- 26/41 (63%) SD
- m TTP 3.8 months
- m OAS 7.1 months
- 1y survival 32%

Xiong et al., JCO 2004, 22: 2610-2617
GEM + Tarceva

- Phase III RCT
- 569 patients
- GEM vs. GEM + Erlotinib
- 1y survival 17% vs. 24%
- Increased non-hem tox
- No difference in EGF-R status
- Rash predicts response

Moore et al., ASCO 2005 #1
Her2/neu

- Herceptin (Anti-Her2/neu) + Gemcitabine
  - N=32 (21% HER2 +)
  - RR 4/18 (24%)
  - mSURV: 7.5 Mo, 1y: 24%

- Phase III-Study ongoing (AIO)
ras-Aktivation beim PDAC

- Mutationen in k-ras onco gene in >80%
- Permanent activation of (small) G-proteins
- Four C-terminal aa form a CAAX-Box
- Recognition signal for Farnesyl-Transferase
  - Thioalkylation of Cystein in CAAX-Box => 1. posttranslational modification
  - Facilitates anchorage of ras in cell membrane
Farnesyltransferase-Inhibitors

- SCH 66336 (Schering-Plough)
- Zarnestra/R115777 (Janssen)
- L-778,123 (Merck)
- BMS214662 (Bristol-Myer Squibb)
FTI Zarnestra

- Phase II Study with R115777 alone
- 20 patienten, chemonaïve, „advanced disease“
- NO Effect (øPR, ø SD)
- Median survival 19.7 weeks (≈ 5 months)
- FTI activity ≈ 50% reduced

- Phase III Studie GEM + R115777 or GEM+Placebo
- 688 patients, chemonaïve, „advanced stage“
- NO significant difference
- Medial survival ≈ 6 months (193 vs. 182 days)

Cohen et al., JCO 2003, 21: 1301-1306
Van Cutsem et al., JCO 2004, 22: 1430-1438
Farnesyltransferase-Inhibitor

- R11577, 2x/d
- Phase II
- 20 patients

Cohen et al., JCO 2003, 21:1301
Enzyminhibitoren

- Pemetrexed (MTA, LY-231514; Alimta™)
  - Inhibitor of multiple folate-dependent enzymes
  - Phase II „promising“
  - Phase III closed
    - See next
GEM plus Pemetrexed

- 565 patients with advanced pancreatic carcinoma
- Randomised phase III-study
- NO Benefit

Richards et al., ASCO 2004 #4007
Tyrosinkinase-Inhibitor

- Phase II
- 25 patients
- Raltitrexed (Tomudex®) 3 mg/m² d1 + Gemcitabine 1.000 mg/m² d1, d8 d21

Kralidis et al., Ann Oncol 2003, 14: 579
Gemcitabine & MMP-Inhibitor

MMP-I BAY 12-9566

- BAY 12-9566 MMP-Inhibitor of MMP-2, -3, -9, -13
- Phase III RCT
  - BAY vs GEM
- 227 Patienten until 2nd interim analysis
- Median survival 3.74 m (BAY) vs. 6.59 m (GEM)

Moore et al. (NCIC-CTG) JCO 2003, 21: 3296-3302
Tumor Angiogenesis

- Tumors express proangiogenic factors
- Tumors have numerous small vessels embedded in stroma
Tumor Angiogenesis

- Vessels, i.e. endothelial cells, proliferate
  - $2^\circ$ VEGF
Bevacizumab

• Phase II-Study
  – Beva 10 mg/kg KG d1 + d15
  – GEM 1,000 mg/m² KO d1, d8, d15
  – 52 patients
• mOS 8.7 months
• 1y survival 29%
• PR 10 (19%), SD 25 (48%)
• Pt. with high serum-VEGF 10.8 months
• Phase III (CALGB 80303) since 06/2004

Kindler et al. ASCO 2004 #4009

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Palliative!
EndoTAG: A New Class of Vascular Targeting Agents

Lipid complexes with positive surface charge

Therapeutics:
- Amphiphilic
- Hydrophobic (Paclitaxel)
- Hydrophilic

Complexation of drugs with EndoTAG (cationic lipid complex)
The Underlying Biology in Blood Vessels

Normal

Transient binding of EndoTAG particles to glycocalyx

Transient binding / No uptake

Tumor

Increased electrostatic interactions of EndoTAG particles with glycocalyx, PS and/or anionic sites at fenestrations / pores

Strong binding / Uptake
EndoTAG®-1 Targets Proliferating Endothelial Cells of the Tumor

EndoTAG®-1 is targeting negatively charged, proliferating endothelial cells
Reduction of Tumor Vessel Density

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<thead>
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<th>Study No</th>
<th>Indication</th>
<th>Dose Levels</th>
<th>Patients planned</th>
<th>Patients admitted</th>
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## Summary for EndoTAG®-1: Clinical Data

<table>
<thead>
<tr>
<th>Patients</th>
<th>151 with advanced, metastatic cancer</th>
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<tbody>
<tr>
<td>Tumor types: Prostate</td>
<td>12 patients (PR 1/12, SD: 1/12) <strong>Response 16 %</strong></td>
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<tr>
<td>GI</td>
<td>33 patients (PR 0/33, SD: 4/33)  <strong>Response 12 %</strong></td>
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<tr>
<td>Breast</td>
<td>36 patients (PR 3/36, SD: 13/36) <strong>Response 44 %</strong></td>
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<tr>
<td>Colorectal</td>
<td>37 patients (PR 1/37, SD: 3/37)  <strong>Response 11 %</strong></td>
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<td>Various</td>
<td>33 patients (only safety information available)</td>
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<td>Dosing schedule</td>
<td>2.6 – 63 mg paclitaxel / m² per single dose</td>
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<td>3 treatments per week</td>
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<td>Duration of treatment</td>
<td>1 – 9 weeks</td>
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<td>Adverse Events</td>
<td>• 75% of reported adverse events were judged related</td>
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<td>• 2 % were judged related and serious</td>
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CT 4001: Overall Study Schedule

- **Screening**
  - Randomization
  - Treatment
    - ≤14d
    - ≤7 wd
    - 7 weeks
    - 1 week

- **Interim Analysis**
  - EoT Visit

- **FU Visits 1 – 6**
  - 8 weeks
  - 48 weeks
CT 4001: Treatment Arms

Wk 1       Wk 2        Wk 3        Wk 4       Wk 5       Wk 6       Wk 7

1
2
3
4

7 days
3 days  4 days

Gemcitabine:
- 1000mg/m²

EndoTAG® -1:
- 11mg/m²
- 22mg/m²
- 44mg/m²
CT 4001: Inclusion Criteria

- Irresectable adenocarcinoma of the pancreas
- Histological confirmation
- ECOG ≤ 2
- ≥ 18 years of age
- Chemonaïve
Tumor Angiogenesis

- Endothelial cells proliferate
  - $2^\circ$ VEGF
  - Upregulate VEGF-R (flt)
Tumor Angiogenesis

- VEGF has been a target for anti-angiogenetic therapy
  - Bevacizumab (Avastin®)

Bevacizumab (Avastin®):
an anti-VEGF antibody

- Recombinant humanised monoclonal antibody targeting the angiogenic factor VEGF
- Similar to Herceptin*: 93% human, 7% murine

© Roche/Genzyme 2004
Bevacizumab in PDAC

Response
The first 5 responses were confirmed by independent radiologic review at the National Cancer Institute

- Evaluable patients: 52
- Partial Response: 10 (19%)
- Stable Disease: 25 (48%)*
- Progressive Disease: 13 (25%)
- Treatment discontinuation: 4**

*Includes 1 unconfirmed PR.
**Includes 2 early deaths (1 GI bleed, 1 bowel perforation), and 2 pts with thromboses requiring treatment discontinuation in cycle 1.

Kindler et al., ASCO 2004
Survival and Time to Progression

- Median survival: 8.7 months (95% CI: 7.3, 9.7)
- 6 month survival: 75% (95% CI: 0.60, 0.85)
- 1-year survival: 29% (95% CI: 0.16, 0.44)
- Median Time to Progression: 5.8 months (95% CI: 4.8, 7.1)

Kindler et al., ASCO 2004
Bevacizumab in PDAC

Kindler et al., ASCO 2004
Bevacizumab in PDAC

Correlative studies

- Mean pretreatment plasma VEGF levels ranged from 0- 461.5 pg/ml (N=42)
- There is no correlation between pre-treatment plasma VEGF levels and response (Kruskal-Wallis test, p=0.23), survival (Log rank test, p=0.23), or progression-free survival (Log rank test, p=0.23)
- Post-therapy VEGF levels were planned, but ongoing work has shown that bevacizumab treatment interferes with the VEGF assay and decreases free VEGF to undetectable levels

Kindler et al., ASCO 2004
Summary & Conclusion

• Medical management of pancreatic cancer
  – conquer of palliation
    ("palliation instead of resignation")

• Treatment modalities must include
  – BSC
    • Adequate pain treatment
    • Nutritional advice/anti-wasting
    • Specials (EPI; jaundice, obstruction, psycho)
  – Antitumor therapy
    • First line & second line Chemotherapy
    • Targeted therapy

• Novel drugs and modalities are on the horizon
Steering group pancreatic cancer

- Manfred Lutz
- Michael Geissler
- Ulrich Graeven
- Volker Heinemann
- Matthias Löhr
- Helmut Oettle

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