Treating Peritoneal Metastasis: Moving Beyond HIPEC

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Moores Cancer Center
November 2006- 57 yo WM presents with change in stool caliber. Colonoscopy reveals rectal cancer at 10 cm from the anal verge and synchronous cancer of the cecum. CT scan reveals mild L hydroureter and associated multiple peritoneal metastases. Tumor moderately differentiated, CEA 22.4. Management?
Outline

• Rationale for cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC)

• Outcomes of cytoreductive surgery CRS and HIPEC for colorectal peritoneal metastases

• UC San Diego experience

• Tumor penetrating peptides to enhance intraperitoneal therapy

• Other future directions
Central hypothesis: In selected patients and tumor types, peritoneal metastases represent the sole site of metastatic disease and therefore may be amenable to aggressive locoregional therapy.
**Peritoneal Metastasis**

Rationale for Intraperitoneal Chemotherapy

- Peritoneal/Plasma barrier allows for high dose
- Peritoneal clearance is less than systemic clearance
- Systemic toxicities may be reduced because of poor systemic absorption

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Yonemura Y. Eur J Surg Oncol 2010;36(12):1131
Hyperthermia Synergizes with Chemotherapy by Inhibiting PARP1-Dependent DNA Replication Arrest

Lea Schaaf¹, Matthias Schwab¹,², Christoph Ulmer³, Simon Heine¹, Thomas E. Mürdter¹, Jens O. Schmid¹, Georg Sauer⁴, Walter E. Aulitzky⁵, and Heiko van der Kuip¹
Peritoneal Metastasis
Evidence for HIPEC

- Is HIPEC beneficial in patients with peritoneal metastasis, or just another bad option?
Colorectal Peritoneal Metastasis
Evidence for HIPEC

- RCT of 105 pts with peritoneal carcinomatosis from colorectal CA to systemic 5-FU vs. HIPEC
  - Control arm: 5-FU x 6 mos, palliative surgery for obstruction allowed
  - HIPEC arm: cytoreductive surgery (CRS), then 90 min HIPEC with MMC, then given adjuvant systemic 5-FU 6-12 wks after surgery x 6 mos
  - 8% mortality in HIPEC arm
  - Only 37% with complete/R1 CRS
  - 12.6 vs. 22.3 mo median OS
- Criticisms
  - Antiquated chemo regimen
  - Included 17% appendix primaries

Verwaal VJ. J Clin Oncol 2003;21(20):3737
Colorectal Peritoneal Metastasis
Evidence for HIPEC

- French cohort study
  - 48 pts underwent CRS/HIPEC
    - oxaliplatin x 30 min ± irinotecan, with IV 5-FU (bidirectional), after neoadjuvant chemotherapy
  - Compared to 48 pts with isolated PC who underwent systemic chemotherapy at centers where HIPEC not available
    - Received FOLFIRI, FOLFOX, capecitabine, or others
  - 23.9 month survival in control arm, 62.7 months in HIPEC arm
Colorectal Peritoneal Metastasis
Evidence for HIPEC

- Largest published series
  - Nationwide Dutch series of 960 HIPECs over 17 yrs, including 660 CRC pts
  - MMC x 90 min
  - 80% with complete/R1 cytoreduction
  - 34% grade III-IV complications, 3% mortality
  - 15 mo progression-free survival (PFS)
  - 33 mo median and 31% 5yr overall survival (OS)

Does HIPEC Actually Matter?

- Randomized trial in recurrent ovarian ca – CRS +/- HIPEC plus systemic therapy n= 120

- HIPEC improved survival in both platinum sensitive and platinum resistant disease

- (26.4 vs. 13.4 mos) No difference in survival in HIPEC arm based on platinum sensitivity

Colorectal Peritoneal Metastasis
French Prodigie 7 RCT

- RCT of CRS vs. CRS/HIPEC with 30 min oxaliplatin (bidirectional), with intraoperative IV 5-FU and systemic chemo in both arms

- Eligibility
  - Isolated PC without liver or lung mets
  - Appendix CA excluded
  - Opened 12/2007
  - 200 enrolled as of 10/2012
  - 264 estimated SS for 80% power to improve OS from 30 to 48 months
  - Primary endpoint: OS
Peritoneal Metastasis
UCSD Approach

• UCSD HIPEC Experience
  • >500 performed since 8/2007
  • 25% for colorectal cancer
  • Median operative time: 7 hrs (3.3-12.5 hrs)
  • Median EBL: 300 cc (50-4000 cc)
  • Median PCI: 13 (2-26)
  • Median PCI of CRC: 8.5 (3-17)
  • 80% CC-0 (84% in CRC), 12% CC-1
  • Median LOS: 10 days (4-36 days)
  • 60 day mortality 1.2%
  • Morbidity ≥ Clavien 3 16%
  • Readmission rate 15%
UCSD Cohort of Patients With Colon and High Grade Appendiceal Cancer s/p CRS/HIPEC

New Approaches to the Treatment of Peritoneal Metastases

• Enhancing drug delivery
  • Tumor penetrating peptides
  • Stromal disruption

• Targeted delivery of radiopharmaceuticals

• Immunotherapy
Tumor Penetrating Peptides

- Identified via phage display- searching for peptides that bind to integrin (alpha V, beta-3, 5) and neuropilin (1,2) receptors that are highly expressed on tumor vasculature and tumor tissue

- Co-receptor for NRP-1, 2 is VEGF- they mediate vascular permeability

- Hypothesis that synthetic peptides could deliver cargo via tumor vasculature deep into the tumor microenvironment
The iRGD peptide and C-end Rule (CendR)

![Diagram showing the interaction between iRGD and CendR peptides with cellular receptors and proteolysis]

- **iRGD** peptide
- **CendR** (CRGDK/R)

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**Cargos**

- Vascular endothelial cells
- Tumor cells

**Internalization**

**Privileged cite for proteolysis**

Tumor specific drug delivery increases anti-tumor effects, while reducing toxicity to normal organs.

iRGD delivers Evans Blue into PDAC in KPC mice

Strong NRP-1 expression in KPC tumors

KPC mice: KrasG12D/+;LSL-Trp53R172H/+;Pdx-1-Cre

iRGD + Evans Blue

Kidney

Spleen

Heart

Liver

Lung

PDAC

PBS + Evans Blue

Mose et al. unpublished data
iRGD peptide induces a tumor-specific entry of co-injected Evans blue

Evans Blue (EB; an albumin-binding dye) was co-injected with various peptides into mice bearing orthotopic pancreatic xenograft tumors. The amount of EB in the tissues was quantified.

*Evans KN et al, Science 328:1031-5, 2010*
KPC mice bearing PDAC were treated with 100 mg/kg Gemcitabine with or without 100 µg iRGD twice a week. The treatment started when tumors became palpable (14-18 week of age).
Stroma-dependent iRGD penetration into PDAC tissue

IV injection of FAM-iRGD into PDAC mice

15 min

30 min

Stromal fibers, FAM-iRGD, Nuclei

de Mendoza TH et al, unpublished data
Tumor-penetrating peptide enhances transcytosis of silicasome-based chemotherapy for pancreatic cancer

Xiangsheng Liu,¹ Paulina Lin,¹ Ian Perrett,¹ Joshua Lin,¹ Yu-Pei Liao,¹ Chong Hyun Chang,¹ Jinhong Jiang,¹ Nanping Wu,² Timothy Donahue,² Zev Wainberg,³ Andre E. Nel,¹ ⁴ and Huan Meng¹

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iRGD Targets Peritoneal Metastases

iRGD Penetration of Peritoneal Metastases is Circulation Independent
iRGD Dependent Drug Delivery Occurs Independent of Circulation

A

IP injection

IV injection

B

Fold over dextran alone

C

Fluorescence intensity normalized to tissue area

PT  SCT  Ht  Lg  Lv  Sp  Pa  Om  Kd

*  **  n.s.  n.s.  n.s.  n.s.  n.s.  n.s.
iRGD Enhanced Delivery of IP Chemotherapy Improves Treatment of Peritoneal Metastases
iRGD Effectively Penetrates Large Peritoneal Metastases from Human Cancers
Conclusions

• iRGD tumor penetrating peptides can enhance drug delivery to peritoneal metastases when delivered IV/IP

• In animal models, iRGD potentiates the effects of chemotherapy in the treatment of peritoneal metastases

• iRGD peptides can effectively penetrate human peritoneal metastases greater than 1 cm in size

• Phase 1 trials of iRGD are in latter stages of development
Hyaluronan-binding peptide for targeting peritoneal carcinomatosis

Hideki Ikemoto¹, Prakash Lingasamy¹, Anne-Mari Anton Willmore¹, Hedi Hunt¹, Kaarel Kurm¹, Olav Tammik², Pablo Scodeller¹, Lorena Simón-Gracia¹, Venkata Ramana Kotamraju³, Andrew M Lowy⁴, Kazuki N Sugahara³,⁵ and Tambet Teesalu¹,³,⁶
Safety and Outcome Measures of First-in-Human Intraperitoneal α Radioimmunotherapy With $^{212}$Pb-TCMC-Trastuzumab

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Purpose: One-year monitoring of patients receiving intraperitoneal... (Am J Clin Oncol 2016;00:000–000)
Peritoneal Metastasis
Additional ongoing research

- Ct DNA in patients with peritoneal metastasis
- Oncolytic vaccinia virus Phase 1
- Laparoscopic approach in patients with limited disease
- Randomized trial of Enterg to reducing length of stay following HIPEC
- Systems biology profiling of peritoneal metastases, placement in appropriate trial of targeted therapy
- Immunotherapy - myeloid cell depletion and adjuvant checkpoint studies (collaboration with Novartis)
- Examining outcomes and associated risk factors
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