ROLE OF REGIONAL THERAPY (HIPEC/PIPAC/IP CHEMO) FOR GASTRIC CANCER PERITONEAL CARCINOMATOSIS

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Disclosures

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Ethicon, Auris, Verb
Opportunities to Improve Survival in GC PC patients

• What is stomach cancer peritoneal carcinomatosis?
• What are the peritoneal carcinomatosis directed therapies in gastric cancer?
• How, when and who of IP /HIPEC/ PIPAC?
  – Intraperitoneal chemotherapy
  – Hyperthermic Intraperitoneal Chemotherapy
  – Pressurized Intraperitoneal Aerosolized Chemotherathy
• How do we select the right therapy for the right GC PC patients?
• How can we do more to achieve a cure for all GC patients?
No Life Should Be Lost to Stomach Cancer
What is Gastric (Stomach) Cancer?

Malignant tumor that arises in the wall of the stomach anywhere from the junction of the esophagus and stomach (EGJ) and the pylorus (the most distal portion of the stomach)
If Left Untreated Gastric Cancer Invades

Cancer cells invade the inner layers of the stomach outward.
...and Spread to LNs and Other Organs

Liver (4-14%)

Lung

Lymph nodes

Omentum
Peritoneum (5-20%)
Peritoneal Carcinomatosis

- Tumors in the peritoneum are called peritoneal carcinomatosis (PC) and associated with many complications
  - Accumulation of malignant ascites
  - Development of bowel obstruction
  - Pain, malnutrition and cachexia
  - Can lead to deaths in weeks to months

- More than 40% of stomach cancer patients 18-40 yo present with Stage IV cancer

- YA are likely to present with PC at the time of initial stomach cancer diagnosis: 32.1% vs. 14.1%
Treatment Strategies for Peritoneal Carcinomatosis

- Usually treated like all other Stage IV disease
- Systemic therapy (FOLFOX, FOLFURI, Herceptin, Pembro, etc)
- These treatments are not enough

**Survival in Months compared to Best Supportive Care (4 months)**

- **5-FU Alone**
  - 7.0 mo

- **Docetaxel + Cisplatin + 5-FU**
  - 9.2 mo

- **Capecitabine + Cisplatin (XP)**
  - 10.5 mo

- **5-FU + Oxaliplatin (FLO)**
  - 10.7 mo

- **Epirubicin + Oxaliplatin Capecitabine (EOX)**
  - 11.2 mo

- **Trastuzumab + CDDP+5FU or Capitabine**
  - 13.8 mo

- **Pembrolizomab MSI-H or dMMR/ PD-L1 +**
  - 2017-2018

**Pembro Chemo Combo**
- CPS ≥ 1: 10.6 vs 11.1 vs 12.5 mo
- CPS ≥ 10: 17.4 vs 10.8 vs 12.3 mo
PC poses distinct therapeutic challenges

- Tumor protective blood-peritoneal barrier and an immunosuppressive environment that prevent effective drug delivery and promote drug resistance
- Diffuse nature of PC makes complete surgical resection ineffective, if not harmful
- Disease often not measurable → Patients do not qualify for clinical trials

**Rationale for Peritoneum Directed Therapy**

- **Blood - Peritoneal Barrier**
- **Metastatic Tumor cell**
- **Immune Aggregates**
- **Cytotoxic T cells**
- **Treg**
- **MDSC**
- **Peritoneal Cavity**
- **Malignant Ascites**
- **Peritoneal Carcinomatosis**
- **Death of Cytotoxic T cells**
- **PD-L1**
Rationale and Goals of Peritoneum Directed Therapy

- Goals of care
  - Decrease tumor burden and improve symptoms from complications such as malignant ascites
  - Complete eradication of tumor in the peritoneum to improve survival (combination of therapies)

- Rationale:
  - To bypass or penetrate the blood-peritoneal barrier: Intraperitoneal chemotherapy can achieve higher concentrations in the peritoneal tumor
  - Heated chemotherapy can penetrate tumor better
  - Repeated dosing is possible and more effective
  - Cytoreductive surgery can have high risk of complications – reserved for those with chance of complete clearance of all tumors
  - Treatment approaches: systemic, intraperitoneal, normal versus heated versus pressurized, cytoreductive surgery or no surgery, what are the best combinations?
Peritoneal Directed Therapy: Lessons from Past Trials

**IP**

Intraperitoneal Chemotherapy

- Trials have failed to demonstrate clear survival benefit IP + IV versus IV alone
- However, responses were encouraging in patients with MA
- Suggested improved survival with IP in high ascites patients

**HIPEC + CRS**

Heated IP Chemotherapy

- 30 years of clinical trials failed to achieve survival benefit for single dose HIPEC in most
- Chemo agents, dosing, timing is varied across the trials
- Benefits patients with occult disease and for improvement of 4 months

**Goals of Care**

Palliative
Preventative
Curative?

- Combination of IV plus IP maybe better
- Earlier treatment of PC is better
- Heated has advantages
- Better strategies are needed
Lessons from Practice-based on Trials

**Systemic chemo plus CRS**
- Multidisciplinary treatment for patients with stage IV gastric cancer: the role of conversion surgery following chemotherapy
- The median OS was 26.0 months.
- Systemic therapy can improve PC

**Systemic chemo plus One HIPEC (one or two chemo agents) plus CRS**
- The median OS was 13.0 months.
  - PCI 0-6 = 18 mo
  - PCI 7-15 = 12 mo
  - PCI 6-39 = 5 months
  - (p = 0.002)
- PCI score matters

**Systemic chemo plus repeat HIPEC (two chemo agents) 5 of 19 CRS**
- The median OS from the date of diagnosis of PC was 30.2 mo, and from the first laparoscopic HIPEC was 20.3 months.
- Systemic therapy can be safely combined with repeat HIPEC and may increase durability of response

Beom, SH et al. BMC Cancer, 2018
South Korea

Rau, B et al. Gastric Cancer, 2019
Germany

Badgewell, B et al. ASO, 2020
Have We Optimized Our PC Treatment Strategy

PreTreatment
Jan 2020

FOLFOX/Herceptin/Pembro
May 2020

Systemic Plus HIPEC#2
August 2020

Poorly Diff, diffuse,
SRC, HER2 (2+);
PD-L1 CPS 5

Systemic Plus HIPEC#3
October 2020

FOLFIRI / Herceptin / Pembro;
November 2020

No HIPEC for 3 months

the MIRACLE of SCIENCE with SOUL – City of Hope
Evidence for PIPAC from International Experts

- 42 Clinical Trials
- Over 800 total patients
- ~200 stomach cancer
- Safe and feasible
- 79% stable disease or decreased ascites
- 10-20 months survival
- May prolong survival
- On-going trials in Europe and Singapore

❖ Phase I Device Registry trial open at COH (T. Dellinger, PI)
• Exactly, what is PIPAC?
  – **Pressurized IntraPeritoneal Aerosolized Chemotherapy**
  – A laparoscopic approach of delivering chemotherapy (or other anti-cancer agents) to destroy cancer cells in the peritoneum
  – Uses a high-pressure drug delivery system **CapnoPen** that is **NOT YET FDA approved in U.S.**

• What is role of PIPAC in the treatment of stomach cancer patients in the U.S.?
  – In its **INVESTIVATIONAL PHASE**
  – Currently undergoing Phase I clinical trial
Phase I Trial In U.S. – PIPAC Device Registry

• To evaluate the safety of the PIPAC device and the method of intraperitoneal delivery of combination chemotherapies by PIPAC

• Indications:
  – Patients with PC from stomach, ovarian, colon and appendiceal cancers
  – High burden of peritoneal disease
  – Progressed on systemic therapy

• Laparoscopic procedure

• Short hospital stay ~24 hr

• Repeat 3 times

Cisplatin
Doxorubicin

Peritoneal Carcinomatosis Index (PCI) Score: 0 to 39
Minimally Invasive and Short Operative Time

Extra-abdominal view

Intra-abdominal view

OR Setup

Extra-abdominal view
Phase I PIPAC Trial: Experimental Design

Experimental Design Schema

Safety and efficacy of pressurized intraperitoneal aerosolized chemotherapy (PIPAC) in ovarian, colorectal, and gastric cancer patients with peritoneal carcinomatosis (PC)
Phase I pilot study (single-arm) = 21 evaluable participants

18 weeks

Registration

Protocol Therapy

Follow-up

• <6 weeks prior to therapy

 PipAC
• 3 treatments given 6 weeks apart

• Tumor response
• Post-operative surgical complications

AE monitoring (primary) 21 weeks

6 weeks

Tumor response

Every 12 weeks

Time to progression (PD also monitored at any time during study)

1 year

Progression-free survival
Potential Role for Regional Therapy in GC PC

At Time of Initial Presentation
Comprehensive Multi-Disiplinary Treatment Strategy

- Diagnostic laparoscopy when safe and able: assess extent of disease, obtain tissue biopsy

- High Risk Cytology +
- Minimal Disease PCI Score <6
- Moderate Disease PCI Score 6-12
- High Burden of Disease PCI Score >12

Standard of Care Guideline-Based 1st Line Treatment Strategy

- Second Line / Clinical Trials / No measurable disease by RECIST

TRIAL: Bidirectional Therapeutic Strategies
- Method of Delivery (HIPEC, PIPAC)
- Agents (chemotherapeutics, immunotherapeutics)
- Mode & Frequency of reassessment

- PIPAC Phase I Device Registry

Outcome: Safety and efficacy
Goal: palliation or curative (improve QoL and prolong survival)
Let’s Summarize the Clinical Realm of GC PC

- Every patient with GC PC should be evaluated by a multidisiplinary team for potential regional treatment option
- Patient-tailored, tumor specific treatment strategy should be developed
- Standard of care is not enough
- Clinical trials of novel therapies and strategies should be considered based on patient’s tumor specific molecular profiles
- Regional therapy with IP, HIPEC, or PIPAC can be considered on clinical trial or on an individualized patient bases (expert centers, experienced surgeons)
  - HIPEC for stomach cancer in clinical trials; and used in clinical practice in select settings
  - PIPAC is INVESTIGATIONAL and undergoing safety evaluation in the United States
  - Phase II trials of efficacy of regional therapy for stomach cancer is planned at COH
- We are striving to bring novel and more effective treatments for GC PC patients
Precision Oncology for GC PC Patient-Tailored Treatment
## Current Clinical Trials Open to Accrual at COH

<table>
<thead>
<tr>
<th>Protocol No.</th>
<th>Allows RECIST Non-measurable disease?</th>
<th>Most Novel Therapeutic Agents being tested IMMUNOTHERAPIES</th>
<th>PI Name</th>
<th>Sponsor</th>
<th>Line of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>20244</td>
<td>No</td>
<td>A Phase 2a, Multicenter, Open-Label Study of DKN-01 in Combination with Tislelizumab ± Chemotherapy as First-Line or Second-Line Therapy in Adult Patients with Inoperable, Locally Advanced or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma</td>
<td>J. Chao</td>
<td>Leap Therapeutics</td>
<td>1L and 2L cohorts</td>
</tr>
<tr>
<td>19311</td>
<td>Yes (during dose escalation)</td>
<td>A Global Phase I Study: Bispecific T-cell Engager AMG199 in Subjects with MUC17-positive GC</td>
<td>J. Chao</td>
<td>AMGEN</td>
<td>≥ 3L</td>
</tr>
<tr>
<td>20052</td>
<td>Yes (during dose escalation)</td>
<td>A Global Phase I Study: Bispecific T-cell Engager AMG910 in Subjects with CLDN18.2-positive GC</td>
<td>J. Chao</td>
<td>Amgen</td>
<td>≥ 3L</td>
</tr>
<tr>
<td>18289</td>
<td>Yes</td>
<td>A Phase 3, Global Multi-center, Double Blind, Randomized Efficacy Study of IMAB362 Plus mFOLFOX6 compared with Placebo plus mFOLFOX6 as First Line Treatment of subjects with Claudin (CLDN)18.2+, HER2-, locally advanced unresectable or mGC or mGEJ AdenoCa</td>
<td>J Chao</td>
<td>Astellas Pharm</td>
<td>1L</td>
</tr>
<tr>
<td>19572</td>
<td>No</td>
<td>A Phase 2/3 Trial to Evaluate Margetuximab in combo with INCMA00012 and Chemo or MGD013 and chemo in patients with mGC or locally adv, treatment-naïve HER2+ GC or GEJ AdenoCA</td>
<td>J. Chao</td>
<td>Macrogenics</td>
<td>1L</td>
</tr>
<tr>
<td>17450</td>
<td>No</td>
<td>PHII-162, NCI#10666: A Phase ½ Study of Olaparib in combo with ramucirumab in mGC and GEJ AdenoCa</td>
<td>J. Chao</td>
<td>ETCTN / NCI</td>
<td>≥ 2L</td>
</tr>
<tr>
<td>18069</td>
<td>Yes</td>
<td>A Phase 1b/2 Trial of the IRX-2 Regimen and Pembro in AGC and Adv GEJ adenoCA</td>
<td>J. Chao</td>
<td>COH</td>
<td>≥ 3L</td>
</tr>
</tbody>
</table>
Future of Novel GC PC Therapies

- Numerous novel agents for cancer are under investigation
- Direct these novel discoveries for stomach cancer patient treatment
- Evaluate these novel agents for stomach cancer peritoneal carcinomatosis in preclinical setting (our laboratories)
- Conduct clinical trials for stomach cancer patients
- Development of better treatment strategies

Plan: Bring best of science and technology to cure stomach cancer patients
The GCWG at COH is a multidisciplinary team of experts in GC / GEJ. We strive to provide the best quality of life and long-term survival for our patients. Our goal is to eliminate deaths due to stomach cancer nationally and worldwide.
Teaming up to cure stomach cancer

- It takes vision, dedication and a team of collaborators to find a cure for stomach cancer.
We are committed

- To eliminate deaths due to stomach cancer (gastric cancer, GC)
- To bring the best of science and technology to improve quality of life and long-term survival for patients with GC
- To develop more effective diagnostic and therapeutic strategies for gastric cancer peritoneal carcinomatosis (GC PC)
Thank you for your dedication and advocacy!

PATIENTS & ADVOCATES

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PSM WORKGROUP

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Small Animal and Small Animal Imaging
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