Punching Above Our Weight: Multi-Center Clinical Trials and the Story of the AHCC Trials Group

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NMRC Senior Clinician- Scientist

NMRC Research Symposium
Grand Copthorne, Singapore 19th March 2015
Singapore is a very small country in a very big continent.

http://en.wikipedia.org/wiki/List_of_Asian_countries_by_population

*United Nations Population Division estimates for 1 Jul 2012
If we are so small
Why should we bother to be thought-leaders in Bio-Medical Science?

• We need to develop the expertise to achieve better outcomes for our own patients
  – Copy from the west/other countries OR
  – Do the research to develop our own expertise

• We want to move up the Bio-Medical value chain
  – The Switzerland of South-east Asia (leader/producer) OR
  – The Bataam of South-east Asia (poor consumer)
Outline

• **Why** multi-center clinical trials

• **Why** Hepatocellular Carcinoma (HCC)

• **A short history** of the Asia-Pacific HCC Trials Group

• The continuing **challenges** and how they are met

• The AHCC Trials Group **infrastructure** platform
Biomedical Research leads to better outcomes in patients

14 days

5 – 8 mm Ø tumours
Biomedical Discovery Cycle

Basic Scientific Discoveries → Translational / Animal Experiment → Phase I → Phase II → Phase III → Better Clinical Outcome

Clinical Insights

Well-conducted *phase III trials* on areas of *pivotal clinical importance* is the fastest and most direct way to bring clinical benefit to patients and influence scientific direction

Adapted from KC Soo
Requirements of a good Phase III trial

- **Thought Leadership**
  - Addresses a pivotal clinical issue the decision of which will impact significantly on clinical practice
  - Good scientific basis
  - Well thought out study design

- **Organization**
  - Good track record and excellent logistical ability to carry out a large trial

- **Large Population Catchment**
  - Large number of patients to provide scientifically robust results – *multi-center trials*
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Hepatocellular Carcinoma: A Global Problem

GLOBOCAN, 2008

sixth most common cancer worldwide, 3rd most common cause of cancer death

SGH – Surgery
HCC is **endemic** in the Asia-Pacific

75% to 80% of cases of HCC occur in the Asia-Pacific
Highly heterogeneous cancer
Collaboration with INSERM

- Application of 100 samples of fresh frozen resected HCC from South-east Asia (Singapore) with a highly annotated database to gene expression analysis, suggest that proportions of European and Asian patients in the different sub-groups are different.

Cannot depend on expertise from the west.

JC Allen et al.

SGH – Surgery
Age-Specific HCC Incidences: USA

In the US, HCC incidences peak at the age of 77.

(El-Serag et al., 2003)

Age-Specific HCC Incidences: Malaysia

(National Cancer Registry, Malaysia, 2008)
Median overall survival in HCC

- Prostate
- Breast
- Colorectal
- Kidney
- Ovary
- Stomach
- Lung
- Oesophagus
- Primary Liver
- Pancreatic
- Leukaemias
- AML
- CML

~ 3-9 month median survival

Percentage of Patients surviving 5 years
Reasons for poor Clinical Outcomes in Hepatocellular Carcinoma

1. **Low research priority.** Historically a cancer of poor people in the 3rd world, previously of little interest to industry.

2. **Highly heterogeneous cancer, wide geographical and genetic diversity** (chronic Hep B vs Hep C?)

3. **Underlying molecular mechanisms poorly understood**
   - absence of proven therapeutic targets
   - absence of robust molecular prognostic classifiers

4. **Few efficacious therapeutics** other than surgery

5. **Paucity of definitive clinical trials**
Hepatocellular Carcinoma: An Unmet Need Globally and in Asia

Surgery is potentially curative in early stage HCC

But 80% are inoperable at time of diagnosis

High recurrence rates
Paucity of therapeutic targets
Lacks molecular prognostic classifiers

SGH – Surgery
Rapid Evolution in the Management of HCC

- The *last decade* has seen better approaches and more efficacious therapies for HCC e.g.
  - Better survival with improved surgical approaches
  - Selective internal radiation therapy with ytium-90
  - Radio-frequency and microwave ablation
  - New systemic therapies

- Resulted in significant improvement in clinical outcomes

- New clinical trials will lead to additional changes in management over the next few years
NEED + EVOLUTION = OPPORTUNITY (TO DO GOOD)
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The Beginning of the AHCC

• Created in 1997 when clinicians from:
  • The Chinese University of Hong Kong
  • The Undayana University, Bali, Indonesia
  • The University Kebangsaan in Malaysia

• Joined an NMRC supported RCT in HCC proposed by:
  • the Dept of General Surgery, Singapore General Hospital (SGH) – no NCCS then
  • NMRC Clinical Trials and Epidemiology Research Unit (CTERU) - SCRI

• The 1st collaborative oncology trial in the region - became truly Asia-Pacific with centers from: Myanmar, Thailand, Australia, Korea and New Zealand

SGH – Surgery
The Asia-Pacific HCC Trials Group

- **Aim**: to carry out definitive multi-centre trials and other research on HCC in the Asia-Pacific where the disease is endemic

- In 1997 - very few therapeutic options for HCC
  - relatively few large clinical studies in HCC

- Clinicians looking after HCC patients in the Asia-Pacific were bonded by a common need:
  - for a trials group that seek efficacious treatment for a common cancer that had few therapeutic options

*SGH – Surgery*
Asia-Pacific HCC Trials Group
40 sites, 17 countries, 1000 patients

- Ulaan Baator
- Hanoi
- Yangon
- Bangkok
- HCMC
- Penang
- Kuala Lumpur
- Singapore
- Jakarta
- Bali
- Seoul, Bundang, Suwon, Suwon
- Taipei, Kaoshiung
- Hong Kong
- Manila
- Davao City
- Brunei
- Melbourne
- Auckland

SGH – Surgery
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**Multi-disciplinary KOLS looking after patients with HCC in the Asia-Pacific**

*Outside of China and Japan*

Kong et al 2013
# Multi-center Clinical Trials of the AHCC

| AHCC01:  | NCT00003424. Randomised Trial of Tamoxifen Versus Placebo for the Treatment of Inoperable Hepatocellular Carcinoma. | 1997 – 2000 NMRC |
| AHCC02:  | NCT00041275. Randomized Double Blind Trial Of Megestrol Acetate Versus Placebo For The Treatment Of Inoperable Hepatocellular Carcinoma. | 2002 – 2007 NCC, SingHealth |
| AHCC04:  | NCT00247260. Phase II dose escalation trial of intra-tumoral Brachysil® in inoperable HCC | 2005 – 2006 PSiOncology |
| AHCC05:  | NCT00712790. Phase I/II Study of SIR-Spheres Plus Sorafenib as First Line Treatment in Patients With Non-Resectable Primary Hepatocellular Carcinoma | 2008 – 2009 NMRC, Bayer, Sirtex |
| AHCC06:  | NCT01135056. Phase III Multi-Centre Open-Label Randomized Controlled Trial of Selective Internal Radiation Therapy (SIRT) Versus Sorafenib in Locally Advanced Hepatocellular Carcinoma (SIRveNIB) | 2010 – 2015 NMRC, Sirtex |
Asia-Pacific Hepatocellular Carcinoma Trials Group

6th General Meeting

31st October 2014

SGH – Surgery
Paradigm Shift: Conducting Clinical Trials in Asia-Pacific

Over the last 16 years

Due to:

• Rapid expansion of pharmaceutical industry
• Potential of new markets in the Asia-Pacific
• Cost effectiveness
  • Relatively cheaper costs of conducting clinical trials
• Improving medical infrastructure
• Reduced amount of regulatory barriers compared to the past
## Multi-center Clinical Trials of the AHCC

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Asia-Pacific is Highly Heterogenous

- Highly diverse geographical region
- Disparate levels of socio-economic development
- Different ethnic populations
- Main burden of HCC
  - high incidences of chronic HBV and HCV
The Advantages of Conducting HCC Clinical Trials in Asia

• Heterogeneity reflects the clinical reality of the disease
  – *Highly representative, achieve definitive outcomes*

• Large number of potential research participants

• Directly benefit patients who otherwise would have no access to new therapies - *Economically disadvantaged nations*

• Opportunities to detect prognostic biomarkers

• Understand various genetic and environmental influences that affect pathology and treatment response
  – *Across different ethnicity and populations*
The Challenges

- Evident gaps in experiences – RCT experience
- Feasibility of conducting good GCP-standard clinical trials
- Rudimentary medical facilities, infrastructure and indemnity assurance
- Differences in the standard of care and cultural practices
  - affect implementation of study protocol
- Funding and Sponsorship Model
Continual Dialogue, Frequent one-to-one meetings and Open Channels of Communications are vital

AHCC06 2nd IM 16/11/12

AHCC06 3rd IM 10/07/14

Challenges are very different in the different countries – one size does not fit all
Meeting the Challenges

• Helping sites to be GCP-compliant
  – *E.g. helping sites to set up IRBs*

• Training of clinical trials teams:
  – *Significant investment in time and resources to train, update and familiarize local staff with study protocol and GCP guideline*

• Thorough audits
  – *E.g. 100% audits for AHCC02 trial*

• Outsource clinical services to privately run institutions outside of the trial centres
  – *E.g. CT scan imaging to meet inclusion criteria*
Extensive Site visits, training, audits

Thailand

Korea

Myanmar

Phillipines

Vietnam
Challenges

• External Challenges
  – Financial, logistical, training, technical,
  – Can be *overcome* with innovation, determination, hard work
  – *Clarity of Vision, Consistency of Purpose*

• Internal Challenges
  – Internal challenges are very difficult to overcome
  – Administrative, philosophical, structural, cultural, fiscal
  – Only *senior leadership* aligned with the mission can resolve them
Funding

• Model of co-funding: academic and industrial sources of funding
  – *Maintain the independence of an investigator-initiated trial*
  – *Increase the quantum of funding available by tapping on industry*

• **AHCC05 (SirSA) - 2008**
  – NMRC $487,000
  – Therapeutics from Bayer ($1mil) and Sirtex ($1 mil)

• **AHCC06 (SirveNIB) - 2010**
  – NMRC $1.67 mil
  – Sirtex $8.5 mil + $1.9 mil
**AHCC06: SIRT versus Sorafenib in patients with locally advanced HCC (SirveNIB)**

Asia-Pacific, Phase III, open-label, randomised-controlled study

**Eligibility criteria**
- Locally advanced HCC
- Child–Pugh <8 pts
- ECOG PS 0 – 1

**Exclusion criteria**
- Distant metastases
- Complete main portal vein thrombosis

**Endpoints**
- **Primary**
  - OS
- **Secondary**
  - TTP
  - QoL
  - Downstaging to curative therapies

**Randomisation**
1:1 (n=360)

- **Sorafenib® 400mg b.i.d.**
- **SIRT**

ECOG PS = Eastern Cooperative Oncology Group Performance Status
OS = overall survival; TTP = time to tumour progression

**Eligible:** Previous surgery, RFA, TACE

*SGH – Surgery*
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Structure of the AHCC
A Collaborative Trial Network

- AHCC Trials Group – a collaborative trials group
- Membership by participation in trials
- Trials governed by a Steering Committee
- Trials managed by an Academic Research Organization (ARO) – Singapore Clinical Research Institute (SCRI), Network Executives and the Protocol Chair
Investigator-Initiated Trials: The AHCC Trials Group Model

Protocol Chair
Steering Committee

Industry e.g. Sirtex, Bayer, GSK

Govt Funding Body e.g. NMRC

Academic CRO
SCRI

CRAs

CRCs Site
Site
CRCs Site
Site
CRCs Site
Site
CRCs

Regulatory Bodies: IRB, DMC

Structure introduces accountability and reduces potential conflict
While trials are initiated by individual PIs they are built from the ground up. Input from sites are crucial important to ensure buy-in.
Developing a collaborative platform

• The AHCC has reached a stage in its development where it is meaningful to develop a collaborative platform with industrial partners.

• To realize this strategic initiative, a collaborative partnership has been developed to facilitate:
  – clinical projects with industry partners
  – funding mechanisms that supports the scientific and administrative infrastructure of the trials group
  – access to the collective expertise of the group on scientific and clinical matters pertaining to HCC
Scientific Forum and General Meeting
31st Oct 2014

Funded through a collaborative platform with industry to become a regular 6-monthly event
Punching Above Our Weight Class

Punching Above Our Weight Class

One dot represents 100,000 people.

SGH – Surgery

http://en.wikipedia.org/wiki/List_of_Asian_countries_by_population

*United Nations Population Division estimates for 1 Jul 2012
**Thought Leadership**
**Organization**
**Large population**

*United Nations Population Division estimates for 1 Jul 2012*

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<td>48</td>
<td>Bhutan</td>
<td>750,000</td>
</tr>
<tr>
<td>22</td>
<td>Taiwan</td>
<td>21,224,000</td>
<td>49</td>
<td>Macau (China)</td>
<td>567,000</td>
</tr>
<tr>
<td>23</td>
<td>Sri Lanka</td>
<td>21,118,000</td>
<td>50</td>
<td>Brunei</td>
<td>413,000</td>
</tr>
<tr>
<td>24</td>
<td>Syria</td>
<td>21,118,000</td>
<td>51</td>
<td>Maldives</td>
<td>324,000</td>
</tr>
<tr>
<td>25</td>
<td>Kazakhstan</td>
<td>16,361,000</td>
<td>52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>Cambodia</td>
<td>14,470,000</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*One dot represents 100,000 people.*

http://en.wikipedia.org/wiki/List_of_Asian_countries_by_population
It is a Virtuous Cycle

Phase III trials are long and tough battles. *I would like to thank all our participating PIs who believe in our science and our vision of what is possible and trust that we can do this* And to the numerous others who have tried to made this easier
But unless we can resolve internal structural and philosophical hurdles, we will be downsized to LIGHT WEIGHT – which is what we really are.
Thank You!

Acknowledgement: Rachel Choi BSc (Hons) for assistance with the slides