Editorial

Tumour Heterogeneity – Impacting Biology Therapeutic Strategies and Outcomes

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This is a very exciting time in cancer medicine for the community of oncologists and cancer biologists as cancer patients begin to utilize the benefits of post-genomic insights to human cancer. Cancer patients have experienced a noticeable improvement in the quality of cancer care, and treatment strategies, as well as the advantages of early and more precise cancer detection. One of the primary contributing factors towards these gains is an increased awareness and personal involvement of cancer patients in their treatment. It is not uncommon to see a self-educated patient visit an oncologist with knowledge of various treatment options and clinical trials.

In spite of these exciting developments, there are obvious drawbacks in meeting the expectations of cancer professionals, even after a decade of human genome sequencing. Such disappointments may also be felt among cancer patients due to limited progress in personalized cancer treatment, a promise of the genome medicine. Both of these areas are further influenced by public discussions of cancer transcriptome as an emerging guideline in making decisions to stratify cancer patients for personalized cancer therapeutics. Among multiple unavoidable reasons for these disappointments include, our far from clear understanding of inherent heterogeneity of a tumour and its microenvironment, bi-directional regulatory interactions between two compartments, and how these events are further influenced by an individual’s lifestyle. It is believed that a combinatorial pairing of these factors may explain the noted variability in the response and treatment outcome while dealing with the same phenotypic cancer and changing cancer statistics in different parts of the world. One of the best examples to illustrate the excitement and limitations of cancer genome is breast cancer.

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OOTR Initiatives

OOTR Investigators Meeting

After the grand opening of the 10th Organisation for Oncology and Translational Research (OOTR) annual conference conjointly held with the 6th Asian Oncology Summit (AOS) on Friday afternoon, OOTP Investigators joined together for an OOTP Investigator meeting to discuss the progress and milestones achieved in the year. Professor Masakazu Tani, President of OOTP, and Professor Louis Chow, Executive Director of OOTP, welcomed investigators from five Asian countries. In the investigators meeting, several completed and active projects were highlighted. The audience jointly reviewed the publication plan of the close-to-completion OOTP-N006 study, a study conducted in Hong Kong and South Korea. Furthermore, the progress of the ongoing OOTP-N007 study, as well as the soon-to-start OOTP-M004 study, were reviewed. Both studies will run in the Philippines and in Hong Kong. In addition to the current clinical research studies, OOTP has several completed clinical projects for which translational studies are in progress. One of these studies is the OOTP-N001 study. The attendants of the investigators meeting discussed on the sample analysis. Another pillar of OOTP has always been education, and the group was introduced to the OOTP Education Program, “Kyoto University, Seoul National University Joint Seminar”. Besides, attendees were informed about the OOTP Journal Collaboration Project with the International Journal of Biomarkers. The final topic for discussion amongst the participants was the formation of OOTP Breast Cancer Collaborative Group (B-COG). This collaborative research initiative recently began and was welcomed with great enthusiasm by the investigators and followed by a valuable discussion on new B-COG projects. The meeting was adjourned shortly after.

References:
1. OOTP-N006: A Randomized Study of mTOR Inhibition by Everolimus in Invasive Breast Cancer Patients after Pre-operative Use of Anthraccline and/or Taxane-based Chemotherapy. NCT01088893
2. OOTP-N007: A Phase II Neoadjuvant Study of Letrozole in Combination with PD-0332991 (Oral CDK 4/6 Inhibitor) for ER Positive, HER2 Negative Breast Cancer in Postmenopausal Women. NCT01070370
3. OOTP-N004: A Phase II Open-label Pilot Study Evaluating the Maintenance Therapy with Exemestane Plus Everolimus after Induction Chemotherapy in Patients with Hormone-receptor Positive Metastatic Breast Cancer. NCT002025712
4. OOTP-N001: A Phase II Study on the Neoadjuvant Use of Chemotherapy and Cetuximab Therapy in Patients with Invasive Breast Cancer
Tumour Heterogeneity – Impacting Biology Therapeutic Strategies and Outcomes (cont.)

One of the earliest recognized contributions of cancer genomic insights comes from the work of Charles M. Perou and his colleagues. Dr. Perou experimentally revealed that breast cancer can be classified beyond IHC nomenclature on the basis of gene expression clusters – each with a distinct tumour behavior and phenotypic readouts. Although microarray approach limits observations to a specific set or sets of probes printed on a given platform, this methodology continues to have practical applications in both basic and clinical cancer research and treatment. This work along with contributions and input from others^{3,4} used a microarray platform to provide the much needed proof-of-concept evidence in early stage breast cancer transcriptomic research, and primed the stage for a large body of work to follow. The next decade witnessed monumental progress in the areas of basic and translational cancer medicine and analytic methods for detecting transcriptomic status methods.

The next turning point in breast cancer genomic research was the use of whole genome sequencing to gain an unparalleled depth of breast cancer transcriptome. Decoding of the digital transcriptome of breast cancer using RNA-sequencing revealed specific global breast cancer transcriptomic alterations and prevalence of variance in triple-negative breast, estrogen receptor positive, and HER2 positive breast cancers$. This approach has not only reassured the notion of genomic heterogeneity, but also provided insights into the underlying basis of heterogeneity to differential splicing and promoter switching. As expected, such findings have opened up the possibility of further fine-tuning the molecular signatures of breast cancer sub-types.

The melting pot of a variety of high throughput sequencing approaches during the last decade continues to be the issue of breast cancer heterogeneity$. Cumulative knowledge from multiple breast cancer studies has raised hope for developing fine signatures for breast cancer sub-types, tracing the lineage of tumour origin, stem-cell versus non-stem cell basis of some breast cancer, revealing the significance of new biologic molecules and pathways in breast cancer progression and treatment$. While cross-comparing cancer transcriptomic studies, it is worthwhile to appreciate an expected, inter- and intra-tumour heterogeneity of cancer sub-types and the fact that most of the tumours initiate as multi-clonal in origin$. This suggested that there is an urgent need to start understanding about the shared elements among tumour sub-types in the background of tumour heterogeneity. To address this issue, a recent report by Prakriti Mudvari et ai took advantage of isogenic TNBC and HER2-overexpressing breast cancer cells and deduced isogenic signatures of two sub-types of breast cancer cells and also validated their findings in pубlically available comparable data sets$.

The on-going revolution in digital cancer transcriptomic research has helped us to unfold, somewhat expected mysteries of cancer cells, but is far from being translated for the benefits of cancer patients. Some of the expected future utility of cancer genomic include predicting and monitoring the sensitivity versus resistance of cancer to a given treatment regimen and on- and off-target effects. The challenge in the field is not to over-recognize tumour heterogeneity, but to start appreciating the similarities amongst patients in a specialized sub-group while making cancer therapeutic decisions.

References:
2. Stein RA. Genetic Engineering & Biotechnology News (GEN) 2014; 34(7):5176
13. Mudvari et al. PLOS One 2013; 8:e74993

Figure 1: Two models of breast tumour progression. Different colors indicate new mutations in the same clone. During mono-clonal progression the tumour follows linear evolution and acquires and accumulates mutations in all cells. Multi-clonal progression proposes that although all cells derive from a single predominant clone, they acquire different mutations. Environmental factors as well as therapeutics could eradicate cells based on certain biomarkers. As a consequence, multi-clonal tumours are more likely to progress and develop resistance, as they are more likely to contain resistant cells to therapeutics. Figure adopted from Kornelia Poljak’s.
Speaker Interview
Research for the Public Good: the Experience of the Asia-Pacific Hepatocellular Carcinoma (AHCC) Trials Group

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On Sunday, Professor Pierce Chow of the National Cancer Center (NCC) in Singapore will give a lecture entitled “Research for the public good: the experience of the Asia-Pacific Hepatocellular Carcinoma (AHCC) Trials Group”. We interviewed Professor Chow on the importance of clinical research on liver cancer, and the Singapore experience.

Q: How was the Asia-Pacific Hepatocellular Carcinoma Trials Group established?
A: The group was formed in 1997 from a collaboration between the Department of Surgery at the Singapore General Hospital (SGH) and the NUS Clinical Trials and Epidemiology Research Unit (CTERU). We started a single centre prospective study in hepatocellular carcinoma (HCC) at SGH. This study quickly evolved into a multi-centre trial in the Asia Pacific Region (APAC) when leading sites from across the region joined the study. We are now an established regional platform focused on preventive and therapeutic studies as well as on translational research. The group shares the philosophy that studies on liver cancer should be carried out in locations where the disease is endemic, where unmet medical need exists, and where patients who would otherwise have no access to new therapies can benefit from participating in the studies. To date more than 30 centres from 14 countries in APAC have participated in prospective studies conducted by the AHCC trials group.

Q: What were the hurdles when you started 17 years ago?
A: When we started, there was hardly any interest from big pharma in studies in the APAC region. Nowadays, many pharmaceutical companies conduct studies across the region, as Asia has become an important market, and costs for conducting studies are still relatively low here. In 1997, it was not common to receive independent research grants for investigator-initiated studies. In addition to funding issues, we also faced the problem of different levels of socio-economic and healthcare development and experience in clinical studies. Many good sites showed interest, but for some, clinical research infrastructure was very lacking. We did a lot of ground-breaking work to help train the sites to enable them to conduct our studies to Good Clinical Practice (ICH-GCP) standards, to give sites access to certain medical equipment, to overcome cultural and linguistic barriers as well as to manage the import of medication. But as a group, we overcame these hurdles and in 2010 we started our 6th prospective clinical trial together.

References:

Immuno-Oncology (I-O) provides insights into understanding the immune system’s role in cancer suppression and into how tumours may evade recognition and attack by the immune cells. It is an evolving science focused on identifying treatment modalities designed to harness the natural capability of the patient’s own immune system to fight cancer. The immune system is complex, made up of multiple mechanisms that act to protect and defend the human body. The immune system can recognize cancer cells as abnormal and mount a defense against them since tumours can express a multitude of proteins, known as “tumor-associated antigens,” that can trigger a tumour-specific T-cell response. The initial stages of the anti-tumor immune response involve the capture of tumour-associated antigens by antigen-presenting cells (APCs). After antigen capture, APCs undergo maturation to become activated APCs that can interact with T cells via cell surface proteins. Activation of T cells requires 2 signals: antigen presentation by the APC and delivery of a second or “co-stimulatory” signal from the APC, to initiate an anti-tumor immune response. There are multiple feedback mechanisms that can affect the immune response by activating or inhibiting T-cell function and proliferation. Cancer cell growth may be associated with an imbalance in the natural feedback mechanisms that lead to a suppression of the immune response.

During the multistep development of various types of cancer, tumor cells may adapt to escape the immune system’s defense mechanisms, which can lead to evasion of immune destruction and to tumour cell growth. Research indicates that tumors may evade cytotoxic (killer) T cells in part by exploiting immune activation and inhibition pathways - essentially “switching off” immune activation and response. Several of the inhibitory checkpoint pathways are targets of clinical research for their role in tumor evasion of the immune system. This includes the CTLA-4 (cytotoxic T-lymphocyte antigen 4) pathway, the PD-1 (programmed death-1) pathway, and the LAG-3 (anti-lymphocyte activation gene-3) pathway.

Pharma Insights
Harnessing the Immune System to Fight Cancer

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One way that tumors can evade normal immune attack is through exploitation of the PD-1 checkpoint pathway via the PD-1 receptor, a key regulator of T-cell activity, by converting active T cells to inactive T cells. The binding of PD-L1 and PD-L2 ligands on the tumor cells to the PD-1 receptor on T cells inhibits activated T cells and suppresses T-cell attack. By blocking the interaction between the PD-1 receptor and PD-L1 and PD-L2 ligands, T-cell activation can potentially be restored, which may play a role in restoring the natural capability of the patient’s own immune system to fight cancer.

*Approaches where there are approved compounds or investigational compounds being studied in phase 3 trials, www.clinicaltrials.gov accessed 26 March 2014.

References:
Short Editorial

New Targets for Colorectal Cancer

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The incidence of colorectal cancer (CRC) remains globally high and difficult to treat. Despite great advances with novel, targeted agents in many solid and haematological malignancies in the past decade, only few but modest improvements in CRC treatment were observed. Although new targets for CRC are currently under clinical investigation, present clinical practice should be focused on optimization of available treatment options, and prevention of CRC.

Compelling retrospective evidence of the efficacy of Aspirin (ASA) and non-steroidal anti-inflammatory drugs (NSAIDs) for the prevention of CRC exists. Rothwell et al.2 published two meta-analyses on pooled data of several cardiovascular disease (CVD) trials in which over 1,000 patients were recruited. The analyses aimed to assess the effect of ASA on a 20-year risk of CRC incidence and mortality, as well as other tumours. The Objective Risk (OR) for patients receiving ASA versus controls in the meta-analyses was 0.66. Furthermore, pooled data by Flossmann et al revealed that regular use of ASA (300 mg/d) reduced the risk of CRC with 26% (p=0.02).3 For patients using ASA for 5 years, the risk reduction was even 37% (p=0.002). Benefit was observed in patients who had taken ASA every day and after a decade’s use.

In a prospective double-blind study by Burn et al., patients with hereditary non-polyposis colon cancer (HNPCC) were randomized to receive either placebo or 600 mg ASA for up to 4 years.4 At a median follow-up of 4.25 years, relative risk reduction for the ASA group was 38%.

It is also evident that ASA is effective in the treatment of patients with CRC and for prevention of recurrence of CRC. Chan et al. recruited 1,279 patients with Stage III CRC from two nationwide cohort studies4. The results showed that patients using regular aspirin after diagnosis of CRC had better CRC-specific and overall mortality (HR=0.71 and HR=0.79 respectively). The efficacy was most clear amongst a subset (N=459) of patients with tumours that overexpressed COX-2. Improved HR for CRC-specific mortality (HR=0.53) was also observed for 719 patients who began taking ASA only following diagnosis.

ASA may also have beneficial effects in the prevention of two other diseases, namely Alzheimer’s disease (AD) and ischemic heart disease (IHD). However, it remains important to balance the risk and benefits of the drug. Long-term use of ASA is associated with several minor side effects5, including heartburn, nausea, vomiting, dyspepsia and abdominal pain. More serious side effects range from mucosal lesions seen on endoscopy or x-ray, to perforated ulcers, severe bleeding requiring hospitalization, small and large bowel ulcer and stricture, and hepatic toxicities. Therefore, log term use of ASA in a preventive strategy should be carefully implemented according to the risk of CRC as well as other diseases (Figure 1) that could help to make balanced decisions for which patients could be suitable for ASA, and for whom the benefits likely outweigh the risks.

Figure 1: Personalized Aspirin Therapy

References:
6. AT Chan et al. JAMA 2009; 302:649-659

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