Editorial

The past, present and future of clinical oncology: an update

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A few years ago, I was invited to speak at the 7th Annual Conference of Organisation for Oncology and Translational Research (OOTR), on the topic “The past, present and future of clinical oncology”. Now, two years after, I am writing to present my thoughts and update in this topic.

Clinical oncology evoked from a subspecialty of medicine whose hallmark was the ability to accurately diagnose the disease and safely treat patients with surgical, radiological and all other anticancer therapies. Currently, this specialty is directly linked to molecular biology, physics and in the future maybe even nano technology. Scientific principles are applied to the prevention, early detection and treatment of cancer patients. The priorities in the development of clinical oncology include study of aetiology and prevention in high-incidence areas, early detection and diagnosis, multi-modality management of cancer patients and trials of new anticancer agents (1). In China, the most important improvements during the past 5 decades were translational research in high incidence areas from simple cancer screening, such as the early liver cancer screening in Qidong county and the studying of cytological abnormalities of esophagus to screen early esophageal cancer and pre-cancerous diseases. Several new drugs or new methods in the management of chorio-carcinoma, APL and testicular cancers were being developed. In recent years, the new developments are new EGFR-TKI (icotinib) and new angiogenesis inhibitors (Endostar and Rg3) (2,3).

Looking back 50 years at the total mortality from cancer, it seems the present situation has not differed too vastly. Cancer is without a doubt still one of the leading causes of deaths in the global population. There are many small steps taken in the path to treat cancer, but no major leaps. We now know, that cancer does not consist of only one single disease, but encompasses various diseases, all housed under one roof. In the past, cancer was thought to be site-specific, divided into such areas of cancers as head and neck cancer, breast cancer, or even stomach cancer, but research has taught us that cancer works on different levels of complexity (4). For instance, breast cancer lays at least five different subtypes that can be distinguished based on RNA genotyping. Distinct genetic differences can also be found in each patient’s tumour. There are hundreds of various types of lymphomas, and at the molecular level, each person’s lymphoma is different (4, 5). Most cancers have over 100 mutations in a single tumour. And if the complexity isn’t enough, some solid tumours display high level of heterogeneity and have different clusters within the tumour that rely on different molecular pathways for proliferation. Although we have gained more knowledge into the complexities of cancer, we are still far from curing the disease. To cure cancer, we would need to cure hundreds, if not thousands of diseases.

A positive note is that we have learned more about cancer in the past decade than we have over the last few thousand years and treatment of cancer had significantly progressed from application of similar chemotherapy and surgery for all oncology patients to personalized treatment for the individual (6, 7). Conventional chemotherapeutic agents work by inhibiting cell division and proliferation, thereby eradicating spreading cancer cells, as well as normal healthy cells, especially those with a high mitotic index such as cells in the hair follicles. A fine line exists between trying to kill the cancer without over harming the patient. And traditionally treating cancer has been a balancing act of the physician delivering the maximum dose of cytotoxic agents to the patient. Newer anticancer agents are more personalized forms of medicine that target receptors, ligands and proteins which are irregularly expressed in cancer cells and drive growth. We even speak of onco-protein addiction when the tumour relies heavily on a single pathway for growth, such as lung tumours with activating EGFR mutations or harbour the EML4-ALK fusion onco-protein. Personalized medicine is available today because of the discovery of molecular biomarkers and their offspring targeted therapies, and the sub-classification of tumours at the molecular level. Biomarkers go beyond routine testing to provide clinicians insight into the current status and behaviour of the cancer and into its prognosis and behaviour in the future. Biomarkers can be used as potential determinants of disease risk, screening, differential diagnosis, prognosis, or treatment outcome. Targeted therapy works to impede the cancer or to prevent it from spreading by targeting the affiliated biomarker (8, 9).

Sequencing the genomes of various cancers has shed light to the fact that there are many more molecular changes than originally imagined. Many cancers are being sequenced and identified.
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today by researchers to look for a list of commonly mutated genes that may be matched with a patient’s tumour (4). Discovering the mutations of patients will allow us to work out the signaling pathways affected by the mutations. Equipped with knowledge about a patient’s gene mutation, we can then apply the correct kinase-inhibitor and block the enzymes involved. Tyrosine Kinase Inhibitors are being prescribed to specifically address mutations in the EGF (epidermal growth factor) receptors, BCR-ABL inhibitors are available for leukemias, while trastuzumab works for a subtype of breast cancers with amplified HER2/neu receptor expression (7). Enzalutamide is an androgen receptor antagonist drug for prostate cancer and finally, we are now also able to direct chemotherapy by monoclonal antibody-drug-conjugates directly to the cancer cell overexpressing receptors such as HER-2 and CD22, and in the near future maybe even by the use of nanoparticles (7-11).

Besides directly attacking tumours, additional success may be gained by attacking a tumour’s microenvironment by cutting off their oxygen and blood supply, which is the concept of antiangiogenesis (10). Understanding tumour stroma, has also allowed scientists to indirectly target tumours by learning its importance for cancer proliferation, development and metastases. Owing to the genetic diversity of tumours, targeting tumour stroma seems an attractive option as it would be independent of the high molecular variance inside tumours (8, 9).

There is still a long road ahead and many more tiny steps to be taken before unveiling the full picture of how cancer works and how it can be eradicated. Before reaching this point, extra emphasis should be placed on prevention programs and education for early detection of oncological diseases. Preventative methods and detection programs that educate the public to be more aware will enable a patient’s cancer to be discovered in the earlier stages.

The dream of oncologists in China will become true may be more than 2 decades later though our efforts to prevent, early detection and treatment, and especially to translate the understanding of cancer in molecular level into individualized management. In that time the etiology and mortality rates will be decreasing significantly like what happened in developing countries currently.

To conclude, I would like to commend the organizers—OOTR and Asian Oncology Summit—for putting forth a fine program and bringing together a top-of-the-class group of researchers, academics, clinical investigators, scientists and clinicians in their respective fields and shining light on an issue that, rising above all else in clinical oncology, should be the main reason we are drawn here together today and to our work every day: “Putting patients first”.

References:

Expert Interview with Ding Shinn Chen

On Friday, Professor Chen gave a lecture on the prevention of Hepatocellular Carcinoma (HCC) by Hepatitis B virus (HBV) vaccination.

According to the World Health Organization (WHO), one-third of the world’s population is infected by HBV. Chronic HBV infection is a main concern, because it is the precursor of HBV-related cirrhosis and subsequent HCC. In the 1970s – 1980s before the vaccination program was implemented in Taiwan, approximately 15-20% of the population in Taiwan was chronic carriers of HBV, and over 80% of chronic liver disease and HCC was caused by chronic HBV infections.

In Taiwan, chronic infections mostly occurred via mother to child transmission perinatally, and via horizontal transmission before the 2nd year in life. The chance of developing a chronic HBV infection later in life is only around 3%.

Taiwan was the first country to introduce HBV vaccination in the Hepatitis Prevention and Control Program that was introduced in 1984. Mothers were tested for the surface marker of HBV (HBsAg) and the extracellular marker of HBV (HBeAg). In the program, all children of HBsAg-positive mothers receive vaccination, and if the mother also tests positive for HBeAg, the child additionally will receive hepatitis B immunoglobulin (HBIG).

Currently, HBV chronic carriers compose 0.5% to 1.0% of the entire population in Taiwan, and the biggest issue is the risk of chronic infections in children born from mothers who have extreme high viral loads. Current research is being conducted in the direction of treating higher viral load-women with anti-viral agents, hoping to reduce the infection levels similar to those seen in most chronic carriers, and to increase children’s susceptibility for the vaccination after birth. These studies may fully eradicate chronic infections in the country.

At present, WHO has initiated vaccination programs in most HBV high incidence rate countries worldwide. The predicted incidence rates of HBV-related HCC in Taiwan will decrease until 2040 as a result of the vaccination program. Other countries and regions with implementation of vaccination programs are likely to follow.
Expert Interview with Nadir Arber

We asked Dr. Arber on the role of COX-2 inhibitors for chemoprevention in colorectal cancer (CRC).

Chemoprevention currently does not have a big role in CRC. In 2004, there was a concern on the cardiovascular risk profile of COX-2 inhibitors, the development of COX-2 inhibitors was set back. This is unfortunate as research has shown that there is a role for aspirin and other COX-2 inhibitors, not only in CRC but also regarding other cancers and even other diseases.

There are three diseases that together make up the biggest health concern of the present time: 1) cardiovascular disease (CVD); 2) Alzheimer disease (AHD); and 3) CRC. Data suggests that COX-2 inhibition can be beneficial in all these three, but of course the patient should be selected based on risk criteria.

An example could be a patient who does not have high risk for CRC, and is without risk indicators such as family history for AHD, but based on the Framingham study this patient has a 20% or higher risk of a cardiovascular event over the following 10 years. Such patients would likely still benefit from aspirin based on the cardiovascular risk profile. However, if the patient is at low risk for all three, aspirin would not be indicated.

There are difficulties. The risk factors for AHD are less well established and it can be difficult to estimate the risk in a patient. One can look at the family history and there are some other indicators that may predict risk as well. Another issue is that we currently know that aspirin may be beneficial for high-risk groups, but we don't know if we should start at intermediate risk for any of these three diseases.

We are currently in the process of investigating whether a study with aspirin is feasible. This will include patients with high risk for any one or more of the three diseases mentioned earlier. This study would not only look at clinical parameters, but also look at about 20 different single nucleotide polymorphisms (SNPs) that may help us predict which patients will benefit from COX-2 inhibition and which patients may have less benefit. Such a study could definitely help us to gain more understanding, and provide compelling data, on how to best use aspirin or COX-2 inhibitors in the clinic. Until this question is solved, colonoscopy remains the most reliable preventative tool we have for CRC, and prevention is the best cure.

Expert Interview with Sumitra Thongprasert

Over recent years there has been a tremendous advancement in the systemic treatment of NSCLC, especially in adenocarcinoma of the lungs. What major advances have there been for adenocarcinoma over the past few years?

The biggest advances have been made in the field of molecular markers. Where we traditionally subdivided lung cancer into different histopathology. Over the past few years we have discovered many prognostic and predictive biomarkers, mainly in adenocarcinoma of the lungs. Among the prognostic markers there are EGFR, ELM4-ALK and KRAS. Predictive markers for response currently include EGFR and ELM4-ALK.

Another major change is that the EGFR targeted therapies (TKIs) have now moved to the front line for metastatic disease and chemotherapy comes in the second-line in patients with known EGFR mutations. Besides EGFR mutations, performance status (PS) is a factor to consider as well. Some data suggests that for patients with poor PS who have an unknown EGFR mutation status, TKI upfront may be beneficial.

Furthermore, it is expected that soon a so called ‘second generation’ TKI will be approved by the United States Food and Drug Administration. There is currently no head-to-head data to compare the new TKI with the existing ones and studies to compare these agents in the first-line setting are underway. Hopefully more data will be available soon to answer the important question, which drug to use in the front-line setting.

For patients with EGFR mutations, or patients who are EML4-ALK positive and who progress on first-line treatment, a second biopsy may give additional information on how the tumor has changed and provide new insight in treatment options.

Although molecular markers have changed the field of lung cancer over recent years, still in about 20% of patients we cannot determine the molecular status after a biopsy and cytology. For such patients, treatment should be based on histopathology, and if histopathology cannot be determined either, care should be provided with prescribing bevacizumab and pemetrexed, as it should be considered that the patient may have squamous cell carcinoma.

For squamous cell carcinoma we are entering carefully into molecular sub-classification as well. It has been found that some patients with squamous cell carcinoma may harbor mutations in the PIK3CA, the catalytic subunit of PI3K. It will be interesting to see if selective PI3K inhibitors will lead to improved disease outcome.

Future research should be directed towards gene signature and proteomics characterization. It may help to classify groups of patients and determine subsequent treatment options.
Pharma Insights

Palbociclib (PD-0332991): A First-in-class CDK 4/6 inhibitor and rational targeted therapy for hormone receptor positive, HER2-negative Breast Cancer

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During the San Antonio Breast Cancer Symposium (SABCS) in December 2012, progression free survival (PFS) analysis of a multicenter, open-label Phase II study of palbociclib plus letrozole in subjects with estrogen receptor (ER) positive and human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer (MBC) were presented by Dr. Richard Finn (1).

Palbociclib is a first-in-class, orally active pyridopyrimidine and highly selective reversible inhibitor of cyclin-dependent kinases 4 and 6 (CDK 4/6). Palbociclib prevents cellular DNA synthesis by prohibiting progression of the cell cycle from G1 into the S phase, as demonstrated both in laboratory models and in early clinical trials. There is a strong link with the action of estradiol on the G1-S phase transition, where it drives transcriptional activation of cyclin D1 (CCND1) leading to formation of the cyclin D1-CDK4/6-Rb complex that facilitates the G1 to S phase transition.

Preclinical studies identified that sensitivity to palbociclib was associated with the luminal ER subtype, elevated expression of cyclin D1 and Rb protein, and reduced p16. In vivo studies exhibited synergistic activity for palbociclib in combination with tamoxifen. Based on these observations, an open-label Phase 1/2 study in combination with letrozole was initiated. The Phase 1 portion (N = 12) established a recommended phase 2 dose (RP2D) of PD-0332991 125 mg QD on a schedule of 3 weeks on 1 week off (3/1), plus letrozole 2.5 mg once daily in three-week cycles.

The Phase 2 portion presented at SABCS 2012 reported two sequential cohorts. Cohort 1 consisted of 66 newly diagnosed hormone receptor positive, HER2-negative MBC patients, while Cohort 2 consisted of 99 newly diagnosed, hormone receptor positive and HER2-negative MBC patients, who were selected for loss of p16 and amplification of cyclin D1. The PFS analysis for the two cohorts combined can be seen in Figure 1.

The data indicates palbociclib used in combination with letrozole substantially improved duration of PFS compared to letrozole alone in patients with ER+/HER2-negative MBC. Moreover, median PFS prolongation in both cohorts was also observed from the interim analysis report. The encouraging results were furthermore supported by consistent effects on objective response rate (ORR) and clinical benefit rate (CBR) within the same randomized trial cohorts.

The safety profile of palbociclib to date has been characterized by manageable and reversible adverse events. The most frequently reported (≥20% of patients) treatment-emergent adverse events (TEAEs) of any grade, regardless of causality were uncomplicated neutropenia, leukopenia, fatigue, nausea, anemia, diarrhea, arthralgia and hot flush. The most frequently reported Grade 3-4 treatment-related TEAEs were neutropenia and leukopenia. There was one Grade 5 event due to disease progression.

A randomized phase 3 study in patients with hormone receptor positive HER2 negative MBC is ongoing.

The Organisation for Oncology and Translational Research (OOTR) is currently conducting the OOTR-N007 study: a phase 2 neoadjuvant study of letrozole in combination with PD0332991 (oral CDK 4/6 inhibitor) for ER positive, HER2 negative breast cancer in postmenopausal women (NCT01709370).

References: