Editorial

Is there a future for PARP inhibition?

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During the San Antonio Breast Cancer Symposium (SABCS) 2012, Puhalla et al. presented promising results from 2 sequential Phase I studies evaluating intermittent Veliparib (ABT-888), a poly-ADP-ribose polymerase (PARP) inhibitor, in combination with either weekly or every 3 week carboplatin and paclitaxel (1). The dose escalation study included patients with advanced solid tumors and was enriched for those with triple negative breast cancer (TNBC). A total of 24 patients with TNBC were evaluable for response; 10 received weekly therapy and 14 received every 3 week dosing. The overall response rate (ORR) in the weekly cohort was 30% (3/10), including 2 complete responses (CR) and 1 partial response (PR), with 3 additional patients achieving stable disease (SD). Fourteen patients received treatment every 3 weeks, with an ORR of 43% (6/14) and SD seen in 2 patients. For the combined population, the ORR was 38% with clinical benefit seen in 58%. Treatment was well tolerated, with dose limiting toxicities including thrombocytopenia and febrile neutropenia.

These intriguing results come at an important time. After a decade of studies with PARP inhibitors, researchers are still trying to figure out how best to employ this class of drugs. This Phase I study demonstrates at least some of the challenges along the difficult road from bench to bedside for PARP inhibitors.

After the successes of imatinib in chronic myelogenous leukemia and trastuzumab in HER2-positive breast cancer, PARP inhibitors seemed to be the next new promising class of agents that could target certain known defects in tumor repair (2). Groundbreaking work by Alan Ashworth’s group showed that BRCA dysfunction and subsequent loss of double strand DNA repair (homologous recombination) sensitizes tumor cells to the inhibition of PARP, which in turn disables the cell’s remaining single strand excision repair (base excision repair (3). In preclinical studies, this combined loss of both major mechanisms for DNA repair led to chromosomal instability, cell cycle arrest and subsequent apoptosis. The effect could be further enhanced by combining the PARP inhibitor with chemotherapeutic agents that damage DNA such as platinum salts, alkylating agents or topoisomerase inhibitors.

How did the concept work in the clinical setting? In 2009 Fong et al. published the results of the Phase 1 dose-finding study of single agent olaparib in patients with disease refractory to standard therapies in the New England Journal of Medicine (NEJM) (4). In this study, 9 patients were known to have germline defects in either BRCA1 or 2, and the majority had serous ovarian cancer or breast cancer. More patients had a BRCA1 than a BRCA2 mutation. Responses (CR and PR) were seen only in patients with BRCA-related disease; 7 additional patients achieved stable disease (SD) of which 2 had BRCA related tumors. However, not all patients with BRCA mutations had clinical benefit from olaparib, perhaps due to acquired secondary mutations in BRCA (5).

A subsequent Phase II study of single agent olaparib in patients with BRCA1 or 2 mutations by Tutt et al treated 54 patients in two dose cohorts, 100 mg BID and 400 mg BID (6). Responses appeared to be dose dependent, with an ORR of 41% in the 400 mg BID cohort and 22% in the 100 mg BID cohort. Subsequent data was less encouraging. At ESMO in 2010, Kaye et al presented results of an open-label Phase II study of 2 different doses olaparib vs. pegylated liposomal doxorubicin (PLD) in ovarian cancer patients with BRCA1 and/or 2 mutations (7). This study failed to show a statistically significant difference in progression free survival (PFS). Gelmon studied olaparib in patients with advanced breast and ovarian cancers, with the only responses seen in those with serous ovarian cancer, which has been demonstrated to have acquired defects in BRCA function (8).

A phase II study of iniparib, a novel agent thought to have PARP inhibitory activity, combined with weekly gemcitabine and capecitabine in patients with advanced TNBC, showed improvement in response, PFS (5.9 months vs 3.6 months) and overall survival (OS; 12.3 months vs 7.7 months) compared to chemotherapy alone (9). However, enthusiasm subsided after the results of a Phase III study with the same design in 519 patients were presented at American Association of Clinical Oncology (ASCO) Annual Meeting in 2011 (10). The study was designed with two co-primary endpoints, PFS and OS. Addition of iniparib did not result in a statistically significant improvement in either endpoint, although an exploratory
analysis of 2nd and 3rd line patients suggested improved PFS and OS in those receiving iniparib. Subsequent extensive pre-clinical studies have demonstrated that iniparib does not actually inhibit PARP at the doses used in these trials (11).

TNBC is defined as negative for the estrogen and progesterone receptors, and without amplification of HER2/neu. Intrinsic RNA subtyping of multiple genes has defined at least five different subtypes of breast cancer. One of these five subtypes is basal-like breast cancer. Most, but not all TNBC, fall into the basal-like subtype. Recent evidence shows that TNBC is not a single disease, but a heterozygous group of tumors of different molecular subtypes (12). TNBC encompasses claudin-low tumors, that mostly resemble the mammary epithelial stem cell (13), basal-like which include BRCA-1 related tumors (12, 13), as well as sporadic TNBC which often have p53 mutations and a high rate of genetic instability (14).

It is believed that tumors displaying DNA aberrations or defects in the DNA repair mechanism, such as BRCA1-related tumors and tumors with loss of P53 such as the basal-like subtype, may be specifically sensitive to agents that cause single or double strand DNA breaks or inhibit the already defective DNA repair system with PARP1 inhibition (14). This suggests that PARP inhibitors could be useful in combination with chemotherapeutic agents in selected patient populations.

Currently, all existing PARP inhibitors are oral agents, and optimal dose and schedule are yet to be determined. Efficacy appears to be limited to patients with known mutations in the BRCA genes, or those with serous ovarian carcinoma. Side effects vary considerably between the different agents, with bone marrow suppression compounded by the addition of chemotherapy resulting in dose limiting toxicity in some initial studies. Why have PARP inhibitors not met with more success in sporadic TNBC? Debate has been ongoing regarding which patients will be most likely to benefit from PARP inhibition. Based on current clinical data, efficacy appears to be improved when PARP inhibitors are combined with chemotherapy agents that themselves induce DNA damage. The study by Puhalla and colleagues is interesting, but as both groups received an effective chemotherapy combination, a subsequent randomized trial would be required to understand the potential additive benefit of veliparib in patients with TNBC. The positive results in early studies of PARP inhibitors do suggest that the drugs can be effective; thus, more clinical and translational studies with further sub-classification of TNBC will be needed to help to identify sub-populations of patients that will benefit from these drugs.

References:
**Expert Interview with Yi-Long Wu**

**Adenocarcinoma of the lung: East meets West**

On Friday, March 22, 2013 Professor Yi-Long Wu, Professor, Guangdong General Hospital and Guangdong Academy of Medical Sciences delivered a lecture in the *Ethnic Differences and Cancer Management* session entitled:

“Special Considerations of Lung Cancer Management in Chinese Patients”.

Over the last couple of years, many mutations and chromosomal inversions (driver mutations) in non-small cell lung cancer (NSCLC) have been identified, and for some of these driver mutations targeted agents are available. We asked Professor Yi Long Wu on the similarities and differences of the overall incidence of driver mutations between Western and Asian patients.

Several studies have been published on the incidence of driver mutations in adeno-carcinoma of the lung. The study data indicate that Asian patients have higher incidence of any driver mutation compared to the Western counterparts. The most notable difference is the frequency of the epidermal growth factor receptor (EGFR) mutations, present in about 40-50% of all Asian patients, whereas KRAS mutations are more common in Western patients (Table 1).

Although remarkable differences exist in the incidence of driver mutations in adenocarcinoma of the lung, there is currently no known cause for these differences. The difference in genetical make-up of Western patients compared to Asian patients is thought to be a possible reason, although there is currently no data to support this hypothesis.

In regard to TKI resistance, patients with activating EGFR mutations are most prone to secondary mutations, which confer resistance to EGFR TKIs. Published literature shows that around 50% of the patients treated with an EGFR TKI will eventually have a secondary T790M mutation. Another tumor escape mechanism frequently seen in patients treated with EGFR TKIs is the activation of another pathway leading to tumor proliferation. cMET and HGF are upregulated in about 20% of EGFR TKI-resistant patients. Finally, some patients will have a small cell lung cancer (SCLC) transformation, and in about 30% of the patients who progresses on TKI, the resistance mechanism is unknown.

Professors Yang and Wu from Guangdong General Hospital have proposed a clinical decision model for EGFR TKI failure. The model divides progression on EGFR TKI into three possible groups: 1) dramatic progression; 2) gradual progression; and 3) local progression. For each group, there is a different treatment strategy to optimize the outcomes of patient (Figure 1) (5).

There are no differences in the applications of diagnostics for Eastern and Western patients, although the use of core biopsies has increased over the recent years with the knowledge of driver mutations and an emerging number of targeted therapies available. Pathology is increasingly important, not only to determine the histology, but also the presence of any driver mutations. However, differences exist for treatment of patients in Asian in comparison to patients in Western countries. Concurrent chemoradiotherapy is commonly employed in Western countries, whereas in Asia, and more specifically in China, sequential chemoradiation is more common. For personalized medicines, the application of targeted therapies, such as bevacizumab is more often prescribed in North American countries such the United States than in Asia. The availability of EGFR TKI is also limited in the United States, where only one EGFR TKI, erlotinib, is available on the market. In a majority of the countries in the East, two EGFR TKIs are available: erlotinib and gefitinib, while China even has a third marketed EGFR TKI, icotinib.

Owing to the differences in Asian and Caucasian lung cancer patients in the areas of epidemiology, etiology and treatment outcomes and toxicities, region-specific clinical trials are certainly necessary to address each of these issues for NSCLC.

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**Table 1: Incidence of adenocarcinoma of the lung driver mutations in different regions**

<table>
<thead>
<tr>
<th>Driver Mutations</th>
<th>LCMC (1) (USA)</th>
<th>MSN (2) (France)</th>
<th>China (3)</th>
<th>Japan (4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>17%</td>
<td>13%</td>
<td>40%</td>
<td>50%</td>
</tr>
<tr>
<td>KRAS</td>
<td>22%</td>
<td>28%</td>
<td>7%</td>
<td>15%</td>
</tr>
<tr>
<td>ELM4-ALK</td>
<td>7%</td>
<td>2%</td>
<td>7%</td>
<td>5%</td>
</tr>
<tr>
<td>BRAF</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>HER2</td>
<td>1%</td>
<td>1%</td>
<td>NA</td>
<td>3%</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>1%</td>
<td>1%</td>
<td>4%</td>
<td>NA</td>
</tr>
<tr>
<td>PTEN</td>
<td>NA</td>
<td>NA</td>
<td>6%</td>
<td>NA</td>
</tr>
<tr>
<td>MET Amp</td>
<td>1%</td>
<td>1%</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>N11</td>
<td>46%</td>
<td>33%</td>
<td>29%</td>
<td>22%</td>
</tr>
</tbody>
</table>

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**References:**
2. Planchard D. Target Oncol 2013;8:3-14.
Expert Interview with Yihai Cao

On Saturday, March 23, 2013 Professor Yihai Cao, Professor of Karolinska Institute, Sweden will deliver a lecture in the Translational Oncology session entitled:

“Mechanistic challenges of antiangiogenic cancer therapy”.

Antiangiogenesis is now regarded as a personalized form of anti-cancer strategies (1). Prof. Cao said, “Angiogenesis was originally the tumor environment proposed by Judah Folkman in 1971. Dr. Folkman proposed that when we suppress tumor angiogenesis, we offer a new option for cancer therapy. It was a very simple, yet very important hypothesis he proposed, although other experts at the time did not support it. In the early 1980s, the first anti-angiogenic effects produced by tumors, including bFGF (now FGF2) and VPF (now VEGF) were discovered. The discovery of these factors suggested that tumors produce angiogenic stimuli to make blood vessels. In 1994, Folkman’s Lab discovered the first anti-angiogenesis factor in the body. It’s a relatively specific one called angiotstatin.”

Prof. Cao introduced several hypotheses on the benefits of combining chemotherapy and antiangiogenic agents for human cancer: “Vascular normalization, as proposed by Prof. Rakesh Jain in Massachusetts General Hospital, occurs when you give an antiangiogenic drug, especially anti-VEGF drug. The disorganized tumor vessels start to present a more healthy phenotype, meaning that the disorganized vessels now become normalized. Normalized vessels actually perfuse more blood, and if you use chemotherapeutics, you may have increased delivery or penetration of chemotherapeutics into the tumor tissues. This is a very attractive hypothesis for the support of combination antiangiogenic therapy with chemotherapy. Our team proposed ‘off tumor targets’ given the fact that many cancer patients may suffer from systemic disease, especially in the late stage of disease. We have experimental models showing that tumor produced VEGF can cause destructive effects in multiple tissues in the laboratory. If you give anti-VEGF drugs to mice, you can actually reduce the tumor-produced VEGF animal destructive effects and improve mice survival by targeting blood vessels outside the tumor. Recently, in a preclinical model, we found both chemotherapy drugs and tumor-induced VEGF targeted bone marrow and induced severe anemia. Anemia is a severe side effect of chemotherapeutics as well. Tumor-induced VEGF also causes anemia. If chemotherapeutic drugs are administered to patients who already have anemia, the situation actually worsens. So, we proposed that anti-angiogenic drugs may actually be able to reduce chemotoxicity. One must remember that a significant number of patients who are treated with chemotherapy will actually die of the toxicity of their therapy. It has been estimated one in four patients may die of the therapy, not the disease. That is a very high number. Imagine if you can reduce patient mortality with a drug. So, the original mechanisms of antiangiogenesis are not as simple as we thought. We have recently published in Nature Medicine (2), showing that activation of stromal cells by PDGF-BB can induce erythropoietin production and that erythropoietin can secondarily induce hematopoiesis rather than inhibit hematopoiesis”. However, the therapeutic benefits of antiangiogenesis are relatively modest in combination with chemotherapy. “Regarding the discrepancies between preclinical and clinical findings and challenges over the clinical use of anti-angiogenesis, Prof. Cao stated, “I will talk more about this in my lecture and in the newsletter to be published post-conference.”

Resistance to anti-VEGF therapy is also challenging for oncologists. Prof. Cao said, “There are many different possible mechanisms: 1) Compensatory resistance mechanism: when you block the VEGF pathway, tumors may use other factors or signaling pathways to make blood vessels. This is particularly true when you try to block VEGF, and the tumor environment becomes more hypoxic and some healthy tissues also become hypoxic. That is what elevates different type of factor expressions including VEGF itself; 2) Vascular mimicry: tumor cells can build up vessels without endothelial cells. These are tubular-like structures and tumors can even perfuse blood with these. When you target or block endothelial cells, but you forget the tumor cells, this mechanism may be activated; 3) Cancer stem cells: they can differentiate into a type of endothelial cells which are resistant to the classical VEGF drug therapy; 4) Tumor stromal cells: anti-VEGF drugs can increase potential stromal fibroblasts compensation and the stromal fibroblasts can produce PDGF-C and in turn stimulate tumor angiogenesis; 5) Recruitment of bone marrow-derived inflammatory cells, neutrophils and microvillus neutrophils: They produce secondarily another set of factors or cytokines, which induce angiogenesis.”

References: