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Biomarkers to Therapy, do they Exist in Hepatocellular Carcinoma?

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In the rapid evolving field of oncology, a large body of evidence points to the importance of predictive biomarkers – a definitive amount of tissue or serum material we can measure and clearly follow to hopefully predict how a cancer patient responds to chemotherapy. We now see that even the same stage of disease in the same type of patients diagnosed at the same age with similar co-morbidities can exhibit diverse biology and therapeutic responses to chemotherapy. What is of most interest to many oncologists is whether we can tell a patient can respond to a certain type of chemotherapy, either traditional cytotoxics or novel targeted agents.

Hepatocellular carcinoma (HCC) is the 3rd leading cause of cancer death worldwide and its incidence in the world, including USA, has persistently climbed over the last 4 decades, largely due to the obesity epidemic and increasing incidence of patients with hepatitis C [1,2]. Alpha fetal protein (AFP) has traditionally been the serum biomarker to increase the suspicion of HCC in patients with risk factors with both sensitivity and specificity below 75% [3], although its utility in predicting effect of chemotherapy in HCC is less well defined.

In the era of pre-sorafenib, various combinations of chemotherapies were studied without benefit of overall survival (OS). Several retrospective studies used various standards to define elevated AFP and AFP responders in patients with HCC. For instance, the patients included for analysis varied from baseline AFP of > 20 ng/ml to > 100 ng/ml and AFP response changed from 20% decrease to 50% decrease [4-6]. Even though such studies showed OS difference in patients who were AFP responders compared to patients without AFP response, the small number of patient in each study, the heterogeneous patient population and definition of AFP response made such data difficult to interpret. Especially when we know none of such chemotherapeutics offered any OS advantage for patients even if patient responded to therapy.

After the introduction of sorafenib, the only FDA approved drug that showed prolongation of overall survival in patients with advanced HCC, a prospective study showed that patients who were AFP responders after 8 weeks of sorafenib achieved longer OS [7]. Unfortunately this study defined abnormal AFP as > 7 ng/ml, which was much lower than the accepted standard of 20ng/ml, leaving the role of AFP as a predictive marker remain undefined. In another study with 53 HCC patients, it defined patient population as those whose AFP > 20 ng/ml and AFP response as > 20% reduction of AFP after 6 weeks of sorafenib [8]. It showed progression-free survival advantage in patients who were AFP responders compared to patients who showed no AFP response, yet it didn't show OS difference among the 2 groups. More importantly, up to 40% of patients with HCC have normal level of AFP at diagnosis [9], thus making it important to search for a predictive biomarker other than AFP.

The true understanding of predictive biomarker in chemotherapy has to come from understanding of cancer biology. In metastatic melanoma, BRAF V600E mutation occurs in up to 50% of tumors and BRAF inhibitor vemurafenib demonstrated not only impressive 50% response rate in patients with BRAF V600E mutation, but it also impressed everyone with stunning overall survival advantage in such patients [10]. The question is, does similar understanding of biology apply to HCC? The answer is yes. Sorafenib is multi-targeted tyrosine kinase that inhibits Raf kinase which is overexpressed in HCCs, the target of Raf pathway is extracellular signaling regulated kinase (ERK), sorafenib also inhibits angiogenesis through various markers such as vascular growth factor receptors (VEGFRs) and platelet derived growth factor receptor (PDGFR) [11]. In the pivotal phase II study of sorafenib in patients with advanced HCC, higher level of phosphorylated ERK (pERK) stained in tissue biopsies before treatment was found to correlate with longer time to progression [12]. Such phenomena was later explained in HCC cell lines where decrease in levels of pERK at baseline led to less growth inhibition by sorafenib [13]. This was an exciting step forward in finding predictive markers to therapy in HCC; although increased baseline pERK levels in retrospective analysis of SHARP study (the randomized phase III study that demonstrated OS advantage of sorafenib in HCC pts) did not show significant improvement of time to progression. The validity of pERK as a predictive marker to sorafenib in HCC is yet to be tested in randomized prospective studies [14] and for the majority of HCC patients whose diagnosis are made without tissue confirmation according to national comprehensive cancer network (NCCN) guideline, a serum predictive marker will be very helpful.

In a plenary session presentation, a retrospective study of sorafenib in SHARP study indicated that sorafenib decreased levels of VEGFRs, although such difference did not translate into prediction of response to therapy [14]. In cancers such as HCC where multiple pathways interface, a single serum predictive marker may underestimate the effects of other potential markers. In a retrospective study of 288 patients, low serum VEGF and high insulin growth factor (IGF)-1 level showed statistically significant longer OS [15]. A study of sorafenib (which provides angiogenesis inhibition) and MDI-573 (an IGF-1 and IGF-2 inhibitor) in advanced HCC is ongoing and results of this study may provide further insights into predictive biomarkers to therapy in HCC.

In a phase II study of sunitinib (a multi-kinase inhibitor that also targets c-KIT, VEGFRs and PDGFR) for HCC patients, it showed OS that was very similar to that of sorafenib phase II study and the correlative studies were fascinating. For instance, lower levels of soluble c-kit and circulating progenitor cells correlated with better

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OS [16]. Circulating progenitor cells originate from bone marrow, it circulates in blood in small quantity under physiologic condition, but it can be mobilized by cancer and is believed to be a critical component to angiogenesis [17,18].

As our understanding of tumor biology continues to advance, predictive markers in cancers such as melanoma already made an invaluable impact for patients and oncologists. Even though a reliable single predictive biomarker in HCC is still not clearly defined, I am optimistic that a panel of serum predictive biomarkers in HCC will be soon available to aid us select the appropriate therapy for patients. As what ASCO president said in ASCO annual meeting in 2010, the future of oncology is "personalized medicine" and HCC will not be an exception.

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