Selected summary for the 2015 Asia–Pacific Primary Liver Cancer Expert Meeting (APPLE)

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Liver cancer is now ranked second in terms of cancer-related mortality worldwide; with limited treatment options for patients at advanced stages it remains a growing health problem. All Phase III clinical trials testing molecular therapies after sorafenib have so far failed, and there is still not a validated oncogene addiction loop. Despite the present huge challenges, advancements in the recent years have been remarkable. The Asia–Pacific Primary Liver Cancer Expert Meeting (APPLE) was designed to promote scientific exchanges of international and regional experts in the study and management of liver cancer. Over the years it has consolidated as a major resource to provide a thorough update to clinicians and researchers located in the Asia–Pacific region in different aspects of liver cancer. Attendance at these meetings is exceptional, with an average of 1000 attendees at each conference. As predicted, the 2015 edition provided an outstanding overview of the latest developments in the clinical management and molecular pathogenesis of the disease.

Osaka (Japan) hosted the 6th edition of the Asia–Pacific Primary Liver Cancer Expert Meeting (APPLE). Perfectly organized by Dr Kudo and his staff, this 6th meeting maintained the spirit and excellence that determined the great success of the previous editions. The scheme of the conference included short and state-of-the-art lectures, poster presentations and consensus statements. Lectures are grouped in themes that cover the whole spectrum of the disease, from hepatocellular carcinoma (HCC) prevention, surveillance, diagnosis, therapeutic approaches (e.g., surgery, loco-regional and systemic) to basic science. Each theme is discussed by a group of commentators that provide context and frame the topic presented within our current knowledge. Herein, I present a brief summary of the some of the main topics discussed during this conference.

Recent updates on the molecular pathogenesis of liver cancer: heterogeneity & the role of gene fusions

One of the most interesting presentations during the meeting was a preliminary report of The Cancer Genome Atlas (TCGA) analyses on HCC, presented by Dr Roberts, from the Mayo Clinic (Rochester, USA). Results confirm previous reports in terms of mutation frequency and DNA copy number aberrations recently reported in large deep-sequencing studies [1,2]. Novel data were presented regarding gene fusions as potentially involved in HCC pathogenesis. There are compelling data demonstrating the oncogenic capacity of FGFR2 fusions in intrahepatic cholangiocarcinoma (iCCA) [3], or the almost universal presence of the DNAJB1:PRKACA chimera in fibrolamellar HCC [4]. Dr Roberts presented some preliminary data on fusion events in HCC samples, including candidates affecting known tyrosine kinase receptors such as MET or FGFR3. Fusions could also induce

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loss-of-function of genes involved in chromatin remodeling such as ARID2. Further validation is still pending to precisely determine the role of these fusions in HCC, but clearly this could provide novel therapeutic targets. In addition, DNA methylation data will also be integrated with these datasets, providing an additional layer of genomic data to complete the landscape of molecular aberrations in HCC. Epigenetic-based signatures have already been shown to correlate with transcriptome-based subclasses [5]. In the same session, Dr Schirmacher from Heidelberg (Germany) highlighted the importance of an integrated and streamlined approach to progressively incorporate molecular read-outs of HCC biology in patient's decision-making, under the 'Umbrella Concept.' This is particularly important for those patients enrolled in clinical trials, where predictive biomarkers are desperately needed. Dr Schirmacher underscored the importance of an interdisciplinary approach for the successful implementation of this concept. In terms of clinical deployment of molecular biomarkers, it will be extremely useful to conduct deep sequencing analysis on stored samples, mainly paraffin tissue. This was addressed by Dr Nishio, who also presented results of a targeted sequencing study using fine-needle biopsies from patients treated with sorafenib.

Another theme that sparked significant attention was the session dedicated to pathological and molecular diversity in HCC. Dr Paradis from Paris (France) reviewed the latest developments in mixed tumors. This entity, despite its low frequency (accounts for less than 5% of all primary liver malignancies), is still difficult to classify. A recent study that included 63 cases found significant variability in terms of the perceptual areas of HCC and cholangiocarcinoma from case to case [6]. Authors developed a histological diversity score based on the different histological components present in each case, which was correlated with features of aggressive clinical behavior such as vascular invasion or AFP levels. She concluded that biphenotypic hepatobiliary carcinoma is an evolving definition that still requires additional refinements under wide consensus. Dr Paradis also suggested that sampling variability in these tumors could impact the diagnostic performance of biopsies. Her lecture set the scene for Dr Yamashita from Ishikawa (Japan), who discussed his recent data on the role of cancer stem cells in HCC. In a recent paper, he described CHD4 as a major

player in maintenance of stemness in liver cancer stem cells [7].

New clinical developments: emergence of immunotherapy

Numerous sessions were dedicated to different aspects of the clinical management of liver cancer patients. Interestingly, the meeting also included face-to-face discussions on the different approaches followed in the East (Dr Kudo from Japan and Dr Ye from China) and the West (Dr Lencioni) to treat patients at intermediate stages. A special emphasis was placed on how to improve patient stratification in terms of risk for HCC development or prognosis prediction in patients who already developed the disease. Improved assessment of the functional status of the underlying liver disease was addressed in the first stage-of-the-art lecture, delivered by Dr Johnson, from the University of Liverpool (UK). He presented the latest results of a large consortium that he is leading trying to evaluate the role of the recently described ALBI grade [8], which utilizes serum albumin and bilirubin, in HCC prognosis stratification by estimating patient's liver (dys)function. Unlike the conventional Child-Pugh score, ALBI only relies on objective parameters and has demonstrated its ability to classify patients based on their prognosis. Dr Chen from Taiwan also discussed the study resulting from the predictive analysis of pooled patients (n = 827) from the SHARP and Asia-Pacific sorafenib clinical trials [9,10]. The objective was to identify predictive factors of benefit to sorafenib, independent of prognostic factors. Variables analyzed included tumor-related (e.g., BCLC stage, vascular invasion, extra-hepatic spread, etc.), background-related (e.g., etiology, age, etc.) and liver condition (e.g., performance status, liver function tests, etc.). It seems that those patients with less tumor burden and no extra-hepatic spread showed a greater magnitude of benefit on sorafenib. Unlike previously believed, etiology did not emerge as an independent predictor of outcome.

Survival predictors in patients that progressed after sorafenib were also discussed. Dr Hsu from Taiwan reviewed recent studies that analyzed which clinical variables are associated with better survival after progression to sorafenib [11,12]. This information will be pivotal when designing second-line clinical trials. Some methodological issues related to clinical trial design were also addressed by Dr Chen from Taipei (Taiwan).

He presented recent proposals on biomarker-based designs, such as the NCI-MATCH initiative. This large study will test 20 different compounds in multiple sites around the USA. Approximately 3000 cancer patients will be screened for 143 actionable mutations and an estimated 30% will be finally enrolled in multiple single biomarker-driven arm trials. Another similar example was recently published for thoracic malignancies [13], which builds upon the concept introduced in the BATTLE trial [14]. This Phase II basket trial enrolled 647 patients that were tested for frequent mutations in lung cancer such as EGFR, KRAS, ALK, etc. Authors concluded that the design was not feasible for rare mutations, what indicates that additional refinements are still needed to implement this approach.

Clearly, one of the most interesting topics presented during the APPLE meeting was the potential role of immunotherapies in HCC. Considering that all clinical trials testing novel systemic therapies in HCC failed to improve or even parallel sorafenib in first line or placebo in second line, the development of novel therapies for these patients is a clear unmet need. The use of immune checkpoint inhibitors (anti-PD1/PD-L1) was recently approved for melanoma and lung cancer [15]. Preliminary results of the nivolumab (anti-PD1/PD-L1 therapy) Phase II trial were already presented during the American Society of Clinical Oncology (ASCO) meeting in 2015. There were eight (19%) patients with objective tumor responses according to RECIST criteria, including two (5%) patients with complete response. In this Phase I/II trial the drug showed a manageable safety profile. The issue of how we could improve response assessment in clinical trials

testing molecular therapies was also mentioned in the state-of-the-art lecture delivered by Dr Llovet (New York and Barcelona). He presented the preliminary results of the assessment of modified RECIST [16] in the brivanib trial in second line [17]. Objective response rate according to this system was an independent predictor of overall survival (full results were presented in the International Liver Cancer (ILCA) meeting on September 2015).

Conclusion

In summary, the APPLE meeting remains as one of the major liver cancer events held in the Asia–Pacific region, attracting worldwide experts in the field and providing an outstanding environment for scientific exchange. The meeting summarized the most recent discoveries related to the molecular pathogenesis of the disease, including some promising new fusions as candidate disease drivers. There is huge expectation to ascertain the role of immunotherapy in HCC in Phase II–III clinical trials. The use of predictive biomarkers was also discussed in this conference, not only referred to anti-PD1/PD-L1 therapies, but also to improve success rate in clinical trials testing molecular targeted therapies.

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