

## Editorial

# Cancer Treatment beyond Progression: is Progression Treatment Failure?

Akiyoshi Kinoshita<sup>1</sup> and Hisao Tajiri<sup>2</sup><sup>1</sup>Division of Gastroenterology and Hepatology, the Jikei University Daisan Hospital, Japan<sup>2</sup>Division of Gastroenterology and Hepatology, Department of Internal Medicine, the Jikei University School of Medicine, Japan

Hepatocellular carcinoma (HCC) is the fifth most frequently diagnosed cancer worldwide and the third leading cause of cancer-related death. An estimated 748,300 new liver cancer cases and 695,900 liver cancer-related deaths occurred in 2008, thus reflecting the poor prognosis of this disease [1]. Advances in treatment including liver transplantation, surgical resection, local ablation, transcatheter arterial chemoembolization (TACE) and the development of the multikinase inhibitor sorafenib, have improved the prognosis of patients with HCC. Among these therapies, sorafenib has been shown to increase the overall survival in the absence of an objective response [2]. The introduction of these molecular targeted agents has raised doubt with respect to the time to progression (TTP) or progression-free survival (PFS) as superior endpoints for detecting the benefits of new agents.

The TTP and PFS indicate the time between treatment initiation and tumor progression or death from any cause, and the post progression survival (PPS) is defined as the overall survival (OS) minus the TTP or PFS [3,4]. In general, the significantly longer TTP or PFS implies an improvement in OS when the PPS is short. However, the statistical benefits in TTP and PFS are lost in OS when the PPS is adequately long [3]. In fact, in recent years, investigators have reported that the PPS is correlated more closely with OS than TTP or PFS in patients with lung, breast, and colorectal cancer and stressed the importance of the PPS in evaluating treatment effects in patients with advanced cancer [5-7].

More recently, in Hepatology (in press), Reig et al. investigated the correlation between tumor progression on imaging modalities and the OS in 147 HCC patients treated with sorafenib [8]. They divided the progression pattern into those involving intrahepatic growth, extrahepatic growth, new intrahepatic lesions and new extrahepatic lesions (and/or vascular invasion). As expected, the OS (median: 12.7 months) was independently associated with the baseline BCLC, registration during follow up of Child-Pugh Grade B or C, the performance status, definitive sorafenib interruption and TTP. Moreover, the authors demonstrated that progression due to the development of new extrahepatic lesions (and/or vascular invasion) is an independent predictor of OS

## \*Corresponding author

Akiyoshi Kinoshita, Division of Gastroenterology and Hepatology, the Jikei University Daisan Hospital, 4-11-1 Izumihon-cho, Komae-shi, Tokyo, 201-8601, Japan, Tel: 03-3480-1151; Fax: 03-3480-6688; Email: aki.kino@jikei.ac.jp

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and PPS in patients with radiologic progression. They concluded that the presence of tumor progression on imaging modalities is significantly correlated with OS and the PPS differs significantly according to the progression pattern. Based on these results, they proposed that the TTP or PFS endpoint should be refined to accommodate the fact that the tumor progression pattern implies a specific impact on the prognosis.

The study by Reig et al. indicates that objective progression does not always suggest treatment failure or the need to change therapy, even in patients with hepatobiliary cancer. As we now face a new age of molecular targeted agents, it is necessary to reassess the criteria for diagnosing progression in cancer patients [4].

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