Ribonucleotide Reductase Subunit M2 Can Be New Molecular Target and Prognostic Biomarker of Hepatocellular Carcinoma

Hee Yeon Kim and Chang Wook Kim

Department of Internal Medicine, The Catholic University of Korea College of Medicine, Seoul, Korea

See “High Expression of Ribonucleotide Reductase Subunit M2 Correlates with Poor Prognosis of Hepatocellular Carcinoma” by Boin Lee, et al, on page 662, Vol. 8. No. 6, 2014

After approval of imatinib for treatment of chronic myeloid leukemia,¹ molecular-targeted therapies make change of the management strategies against cancers. Many target molecules have been revealed in several cancers such as lung cancer, breast cancer, colorectal cancer, and hematopoietic tumor. Representative molecular-targeted agents are trastuzumab for breast cancer, imatinib and rituximab for hematopoietic tumors, and gefitinib and erlotinib for lung cancer. These molecular-targeted agents improved patient's survival and life quality. Hepatocellular carcinoma (HCC) is one of the popular cancers in the world. The prognosis is still poor even though we have tried to detect it at early stage and treat it properly with numerous treatment modalities such as transarterial chemoembolization (TACE), radiofrequency ablation (RFA), systemic cytotoxic chemotherapy, surgical resection and liver transplantation. Now, we have only one approved molecular-targeted agent against advanced HCC with limited efficacy, which is sorafenib as an inhibitor of tyrosine kinases such as the vascular endothelial growth factor receptor (VEGFR) and platelet derived growth factor receptor (PDGFR).^{2,3} Unfortunately, the carcinogenesis pathway of HCC is not clear compared to other cancers. Several targets such as VEGFR, PDGFR, epidermal growth factor receptor, fibroblast growth factor receptor, and mammalian target of rapamycin (mTOR) were investigated recently and several molecular-targeted agents such as brivanib, sunitinib, linifanib erlotinib and everolimus were clinically studied but, the results were disappointing.⁴ Some signaling pathways including growth factor pathway, Jak/Stat pathway, Akt/mTOR pathway, Hedgehog pathway, Wnt/ β -catenin pathway can be molecular targets for treatment of HCC.⁵ Although great efforts have been made for

looking out the unique target molecule of HCC, we don't know the proper molecular targets of HCC which can be investigated for the development of new molecular-targeted agents. So, we need new effective molecular target of HCC, when it blocked, it improves patient's survival and life quality, as other tumors were treated with their own molecular-targeted agents. Several international clinical guidelines recommend the diagnosis criteria of HCC without liver mass biopsy in selected conditions.⁶⁻⁸ Because of these diagnosis criteria, liver mass biopsies have been decreased dramatically compared to past decade. These diagnosis strategies of HCC without biopsy improve clinical convenience and we can avoid the complications of liver biopsy especially in patients with cirrhosis such as bleeding and tumor seeding. But, we lose the opportunity for getting HCC tissues. Without tissues, we could not progress in molecular classification of HCC. And we could not find the unique molecular targets for HCC. From these perspectives, the article titled “High expression of ribonucleotide reductase subunit M2 correlates with poor prognosis of hepatocellular carcinoma” by Lee et al.⁹ has several meaningful messages. First, Ribonucleotide reductase subunit M2 (RRM2) could be target molecule of HCC, which is another field of target molecule in HCC. It is essential for DNA synthesis therefore inhibition of RRM2 could stop DNA synthesis and cell proliferation.¹⁰ RRM2 could be considered a promising target for HCC therapy. Second, RRM2 overexpression could induce nuclear factor- κ B activation and matrix metalloproteinase-9, which enhance invasiveness of HCC. So, RRM2 overexpression is reasonable marker of early recurrence of HCC. RRM2, as biomarker of invasiveness, is meaningful independent factor for prognosis after curative resection of HCC

Correspondence to: Chang Wook Kim

Department of Internal Medicine, Uijeongbu St. Mary's Hospital, The Catholic University of Korea College of Medicine, 222 Banpo-daero, Seocho-gu, Seoul 137-701, Korea

Tel: +82-31-820-3997, Fax: +82-31-847-2719, E-mail: cwkim@catholic.ac.kr

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and similar with pathologic feature such as tumor size, micro-vascular invasion and intrahepatic metastasis. If we have more valuable biomarkers of HCC for prognosis, we could do better decision making for patients care. We need more prognostic biomarkers for improving patient's survival and proper management of HCC. Third, tissue study is mandatory for improving molecular classification of HCC, which is the weak point of HCC compared to other cancers. We need more liver mass biopsies or tissue specimens for investigation of the proper and unique target molecules of HCC.

The introduction of sorafenib was the start of paradigm shift of HCC treatment, but recent disappointing results of several molecular-targeted agents against HCC persuade us to find out new targets of HCC. We need to get liver biopsies or specimens for tissue studies and molecular classification of HCC, which could be the start of investigation for new targets and biomarkers of HCC. It will develop the management strategy of HCC in the era of molecular-targeted therapy.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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