



MAY GLYPICAN-3 BE A NOVEL BIOMARKER AND POTENTIAL THERAPEUTIC TARGET IN HEPATOCELLULAR CANCER?

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SUMMARY

The burden of advanced chronic liver disease is increasing worldwide, despite the recent advances in the management of chronic hepatitis viral infections. The abdominal ultrasound is the only approved method for surveillance of patients with cirrhosis, a premalignant condition for hepatocellular cancer (HCC). Although alpha fetoprotein has been known as a tumour marker for HCC, it is not commonly used for screening due to suboptimal sensitivity and specificity. There is a need to introduce a novel biomarker for definition of HCC in early stage and for prognostic and therapeutic response assessment. A review of the current evidences, encouraging the use of glypican-3 in management of patients with cirrhosis and HCC is presented.

Keywords: hepatocellular carcinoma, cirrhosis, biomarkers, glypican-3,

BACKGROUND

The evaluation of the focal liver lesions in the patients with advanced chronic liver diseases is an important and challenging clinical problem. Liver cirrhosis is frequently associated by various spectrum of nodules, that may follow the multistep transition from large regenerative nodules to low-grade dysplastic nodules and high-grade dysplastic nodules, leading to development of early to progressed hepatocellular carcinoma (HCC) [1]. Exactly the HCC is a major cause of mortality between the patients with compensated advanced chronic liver disease [2, 3].

The ability to detect and diagnose the early HCC (small well-differentiated HCC of vaguely-nodular type, single lesion ≤ 2 cm, T1) is essential. Curative treatment, such as resection, ablation and liver transplantation, achieves 5-year survival rates range from 60% to 80% [4].

Currently, backbone of HCC detection, staging and assessment of treatment response is the imaging studies. The abdominal ultrasound (US) is a first-choice modality, the only approved test for 6-month surveillance of high-risk patients for HCC [5, 6]. This widely available method, however, requires an expert examination due to inhomogeneous and nodular pattern of cirrhotic parenchyma as well as ill-defined margins of early HCC. The sensitivity of conventional US for detection of small HCCs is 65% to 80%. As a screen method and a possibility of over-diagno-

sis, every new detected lesion by US should be further investigated with contrast-enhanced US, computed tomography and/or magnetic resonance imaging. European Association of the Liver (EASL) recommends at least two contrast-enhanced imaging techniques with typical for HCC findings for correct diagnosis of nodules, sized between 1 and 2 cm and excludes the use of contrast enhanced US, due to lower specificity for HCC [5]. The hallmark of HCC is a hyper-vascularization observed in arterial phase with progressing hypo-enhancement during the portal venous phase or delayed phase of contrast-enhanced imaging. **This dynamic “wash-in and wash-out” characteristic identifies the HCC with limited sensitivity, but with close to 100% specificity in the patients with liver cirrhosis. In the absence of typical appearance, a biopsy is required to diagnose HCC** [4, 5, 7]. Overall, the guided biopsy has 30% false negative results in established small HCC [8]. Therefore, a need for accurate and non-invasive biomarker is apparent.

The biomarkers are molecules crucial for the clinical decisions in different ways: as a cut-off helping to identify the presence of the disease and as a monitor of its progression and treatment efficacy. The concentration and dynamics of alpha-fetoprotein (AFP) is a standard, commonly used biomarker for HCC. The AFP is a glycoprotein produced by the foetal liver and yolk sac during pregnancy. Elevated AFP has been documented in acute hepatitis, severe flare of chronic hepatitis, active liver cirrhosis, and neoplastic disorders as HCC, cholangiocarcinoma, hepatoblastoma, nonseminomatous germ cell tumours. The elevation of AFP in the persons with cirrhosis could be a sign for development of HCC. At a cut-off value of 20 ng/mL of serum, AFP shows a 60%–80% sensitivity in detecting HCC, that decreases to about 40% for the detection of tumours smaller than 3 cm. **Only 10-20% of early HCCs are presented with abnormal AFP.** Thus, the AFP level is not included in algorithms for surveillance and for diagnosis of HCC in Europe [5, 6]. Despite that, AFP is a general part of evaluation of patients with cirrhosis or focal liver lesions in clinical practice. **The consistent increase of serum AFP above 300 ng/ml are indicative of HCC.** High AFP levels (as cut-off of 200 ng/ml or 400 ng/ml) have been shown to have independent prognostic value in large cohorts of untreated advanced HCC tumours and have a role as predic-

tor for response to loco-regional therapies, but the significance of AFP was not assessed in control studies [4].

Many other markers have been studied in order to replace or complement AFP, but are not validated. Among them are: lens culinaris agglutinin-reactive AFP (AFP-L3, which is the glycosylated isoform of AFP); prothrombin induced by vitamin K absence II (PIVKA II or des-gamma-carboxy prothrombin, DCP); glypican-3 (GPC3); osteopontin; Golgi protein 73; squamous cellular carcinoma antigen.

REVIEW RESULTS

Glypican-3 (GPC3) is an onco-foetal protein, like AFP [9]. This interesting molecule is a part of family of proteoglycans, attached to the cell surface through a glycosylphosphatidylinositol anchor. Overall, glypicans act as co-receptors by facilitating the formation of ligand-receptor complexes and effectively lowering the required concentration of ligands. Glypicans can also be found extracellularly, after being released by a lipase that cleaves their anchors [10]. Cytoplasmic translocation and over-expression of GPC3 was found in a variety of cancers, typically HCC, and rarely in metastatic colorectal carcinomas, alpha-fetoprotein-producing gastric carcinoma, hepatoblastoma, Wilms' tumour, malignant melanoma, choriocarcinoma, ovarian cancer, and pancreatic ductal adenocarcinoma. **Recent studies discover the role of GPC3 in promoting cancer proliferation and development.** GPC3 regu-

lates signal pathways, including Wnt, Hedgehogs, bone morphogenetic proteins, and fibroblast growth factors. GPC3 has been shown to activate the canonical Wnt pathway in 18% of HCC and subsequent accumulation of β -catenin in the cytoplasm [10]. GPC3 also binds to insulin-like growth factor-II (IGF-2) and its receptor (IGF-1R), mediating enhancement of IGF-related signalling, cell proliferation and prevention of apoptosis, thus supporting the HCC carcinogenesis [11].

GPC3 has been studied both as a biomarker for HCC and as a therapeutic target [9, 10, 12]. Here, a current data on the utility of GPC3 in the management of HCC will be discussed.

The role of GPC3 for detection of HCC

GPC3 mRNA is upregulated significantly in tumour tissues of HCC compared to absent or weak expression in the surrounding liver cirrhotic and non-cirrhotic parenchyma. GPC3 mRNA levels were more frequently elevated in HCC tissue, than those of AFP (88% versus 55%), and the difference was even greater in HCCs smaller than 3 cm (77% versus 43%) [13]. Strong expression of GPC3 protein has been found in a large proportion of the cases with HCC (Table 1). The staining pattern is mainly cytoplasmic but may be membranous or rarely canalicular [10, 14]. In general, the studies reported for high GPC3 expression if the percentage of positive tumour cells by immunohistochemical staining was above cut-off of 10% or the expression level was scored semi-quantitatively as "+3" [15].

Table 1. Glypican-3 expression in tissues and serum in patients with hepatocellular carcinoma, compared to chronic liver disease and other liver neoplasm.

Authors and year of reference publication	GPC3 in HCC		ICCN N (%) positive staining	Non-malignant liver tissue	
	Tissue GPC3 N (%) positive staining	Serum GPC3 mean level ng/ml		Adjacent tissue N (%) positive staining	Cirrhosis N (%) positive staining
Hsu HC, et al, 1997 [13]	143 (74.8%)				
Capurro M, et al, 2003 [14]	21 (72%)			0%	
Anatelli F, et al, 2008 [16]	36 (49%)			0%	0%
Shirakawa H, et al, 2009 [17]	36 (78.3%)		0%		
Liu H, et al, 2010 [18]	55 (94.8%)			0%	0%
Zhang L, et al, 2012 [19]	205 (87%)		0%	0 (0%)	
Chen IP, et al, 2014 [20]	28 (50.9%)				
Sideras K, et al, 2015 [21]	52 (39.1%)			0%	
Cui X, et al, 2015 [22]	74 (71.2%)			0%	
Kaseb AO, et al, 2016 [23]	47 (84%)				
Jeon Y, et al, 2016 [24]	153 (82.7%)				
Ofuji K, et al, 2017 [25]	13 (56.5%)	346.2			
Sun B, et al, 2017 [26]	55 (72.4%)	272.5		3 (3.95%)	

Abbreviations used in table 1: **GPC3** - Glypican-3, **HCC** - hepatocellular carcinoma, **ICCN** - intrahepatic cholangiocarcinoma, **N** - Number.

According to these data, the tissue GPC3 positivity seems useful to differentiate premalignant lesions from well-differentiated HCC. **European Society for Medical Oncology (ESMO) Clinical Practice Guidelines recommended immune-histochemical assessment of the suspected for HCC tissues: GPC3 staining to differentiate high-grade dysplastic nodules from early HCC; cytokeratin 19 (CK19) to progenitor cell features or biliary origin in the mixed forms of HCC/cholangiocarcinoma and CD34 staining to assess neovascularization** [27]. Because the HCC is a heterogeneous tumor and the GPC3 expression may be focal, a panel of markers should be necessary. The combination of heat-shock protein 70 (HSP70), GPC3 and glutamine synthetase (GS) has been recommended by EASL as a standard panel for immunochemical staining to distinguish HCC from dysplastic nodules and other liver malignancies and to confirm diagnosis of HCC [5]. Importantly, cholangiocarcinoma showed negative expression of GPC3 [17, 19].

The expression of GPC3 in the serum of HCC patients (at both mRNA and protein levels) was significantly higher than in the serum of healthy adults or patients with non-malignant liver disease. Meta-analysis of 17 studies on serum/plasma GPC3 revealed pooled sensitivity of 56% (95% confidence interval, CI 53-59%) and specificity of 89% (CI 87%-90%) for diagnosis of HCC [28]. A soluble form of GPC3 can be detected in the serum of 40-53% of HCC patients, in 50% of AFP negative HCC and in 33% of HCC patients seronegative for both AFP and DCP. **The level of GPC3 has not found to be correlated to the serum concentration of AFP [29]. The combination of both GPC3 and AFP concentration tests increases the detection rate of HCC to 72%-85%** [26, 29]. Importantly, serum GPC3 concentration has also been found to correlate with immunohistochemistry detection in HCC tissues (measured by scoring system or as an area GPC3 positive liver tissue) [15].

The role of GPC3 for diagnosis of early HCC and surveillance of patients with cirrhosis

As stated by International Consensus Group for Hepatocellular Neoplasia (ICGHN), tissue GPC3 immune reactivity has a reported sensitivity of 77% and specificity of 96% in the diagnosis of early HCC; therefore, GPC3 positivity is a strong argument for malignancy [1]. GPC3 is superior to AFP in early detection of HCC [12, 18]. According to Ofuji et al., the cut-off value of 132 ng/mL of plasma GPC3 has 40.0% sensitivity and 92.3% specificity for early (stage I) HCC. The sensitivity of the combination of all three markers (AFP, PIVKA-II and GPC3) was increased to 88.0% [25]. Another study from Asia assessed sensitivity of 46.7% and specificity of 93.5% at the cut-off value of GPC3 of 300 ng/ml for diagnosis of HCC. Among the 32 clinically diagnosed liver cirrhosis patients, the serum GPC3 level was > 300 ng/mL in 9.4%. Among the early HCC patients, 7 (50%) had GPC3 level above the diagnostic threshold of 300 ng/ml [18]. Although the number of studied patients were small, the authors concluded that the GPC3 serum test may be a useful marker for an early HCC. However, the sensitivity of the test is not

sufficient for surveillance recommendation.

GPC3 as a marker for invasiveness and prognosis of HCC

The GPC3 tissue positivity correlated with poor prognosis and is identified as an independent prognostic factor for the overall survival (OS) of patients with HCC, for early HCC recurrence after resection and probably worse prognosis of the patients after liver transplantation (LT) for HCC [22-24, 30, 31]. Two recent meta-analysis, including more than a thousand patients with HCC showed that the high GPC3 expression predicted poor OS and disease free survival (DFS) [15, 32]. The GPC3 over expression was significantly associated with the high tumour grade (odds ratio, OR: 3.30, 95% CI: 2.04-5.33), the late TNM stage (OR: 2.26, 95% CI: 1.00-5.12), and the presence of vascular invasion (OR: 2.43, 95% CI: 1.23-4.82) [15]. A cohort of 104 HCC patients with hepatitis B viral cirrhosis who had undergone LT was studied. GPC3 was an independent risk factor for 5-year survival rate and DFS rate, together with tumour differentiation, Milan criteria and pre-operative AFP [22]. The tissue GPC3+ rate obviously increased following clinical upstaging, according to recent study from 37.3% (6/16) in stage I to 92.9% (26/28) in stage III HCC [26].

GPC3 may be involved in stem cell biology in HCC. SALL-4, Spalt like transcription factor, involved in the maintenance of embryonic and cancer stem cells has recently been shown to be expressed in an HCC subtype with stem-cell like features and to be associated with poor prognosis. The study of Sideras et al. showed that the patients with co-expression of high levels of both GPC3 and SALL-4 have worse HCC-specific survival [21]. Another study reported for significance immune-phenotype of HCC as factor for invasiveness. Cohort of 198 patients with HCC within Milan criteria achieved radical resection; independent predictors for HCC recurrence were found to be the CK19+/GPC3+ co-expression pattern, the histological grading and multifocal distribution [33]. **The positivity for CK19 and GPC3 confirmed the possible origin of HCC from hepatic progenitor cells. However, up to now, there is no approved sub-classification of HCC, according to expression of tissue biomarkers.**

GPC3 serum level for monitoring and definition of treatment response and recurrence

The importance of serum GPC3 dynamics was studied in several trials, predominantly in patients treated by radical resection. Usually, GPC3 levels were significantly decreased after operation. High levels of preoperative GPC3 have been documented to predict postoperative recurrence [24, 25, 31]. Only 18.2% of patients with HCC without recurrence of the tumour had preoperative level of GPC3 above cut-off of 132 ng/ml, compared to 57.1% positive rate in the recurrent group. None of the patients with radical treatment and DFS after a median follow-up of 2.8 years had postoperative level of GPC3 >132 ng/ml. Postoperative plasma GPC3 positivity (GPC3 >132 ng/ml) was significantly correlated with worse recurrence-free survival [25]. **Anyway, large patient's cohorts are needed to further investigate that promising biomarker for monitoring the post-therapy evolution.**

CONCLUSIONS

Tissue glypican-3 positivity is a strong argument for malignancy. Glypican-3 serum test may be a useful marker for detection of HCC, providing data complementary to alpha fetoprotein investigation. However, the sensitivity of the test is not sufficient for surveillance recommendation in patients with advanced chronic liver disease. Further studies are needed to confirm the prognostic and therapeutic capabilities of this promising biomarker.

Abbreviations:

AFP - Alpha-fetoprotein; **CD** - cluster of differentiation; **CI** - confidence interval; **CK** - cytokeratin; **DCP** - des-gamma-carboxy prothrombin; **DFS** - disease free survival; **EASL** - European Association of the Liver; **ESMO** - European Society for Medical Oncology; **GPC3** - Glypican-3; **HCC** - (hepatocellular carcinoma); **IGF** - insulin-like growth factor; **ICGHN** - International Consensus Group for Hepatocellular Neoplasia; **ICC** (intrahepatic cholangiocarcinoma); **LT** - liver transplantation; **N** - number; **OR** - odds ratio; **OS** - overall survival; **PIVKA II** - prothrombin induced by vitamin K absence II; **RNA** (ribonucleic acid); **SALL-4**, Spalt like transcription fact; **US** - ultrasound.

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