Somatostatin receptor expression in hepatocellular carcinoma: prognostic and therapeutic considerations

Omar Abdel-Rahman, Angela Lamarca1, Juan W Valle1,2 and Richard A Hubner1

Clinical Oncology Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt
1Department of Medical Oncology, The Christie NHS Foundation Trust, Wilmslow Road, Manchester M20 4BX, UK
2University of Manchester, Manchester Academic Health Sciences Centre (MAHSC), Manchester, UK

Abstract

Sorafenib is the only systemic therapy to demonstrate a significant survival benefit over supportive care in robust randomised controlled trials for advanced hepatocellular carcinoma (HCC). In the context of an intense search for prognostic and predictive factors for response and efficacy of different systemic therapies (including sorafenib), a number of molecular targets have been identified, paving new avenues for potential therapeutic opportunities. Such molecular targets include somatostatin receptor (SSTR)-related alterations. In this review, we provide an overview of the various considerations relating to SSTRs as potentially novel prognostic and predictive biomarkers for HCC with special emphasis on the therapeutic potential of somatostatin analogues in HCC management.

Key Words
- hepatocellular carcinoma
- somatostatin receptors
- somatostatin analogues
- octreotide
- lanreotide

Introduction

Hepatocellular carcinoma (HCC) is a global health problem as it is the sixth most common cancer in the world and the third leading cause of cancer-related death. The incidence of HCC shows wide geographical variation with Western countries having an annual incidence of ~3 per 100,000, rising to 15 per 100,000 in parts of Africa and Asia (Parkin et al. 2005). This variation closely mirrors the geographical distribution of viral hepatitis B (HBV) and hepatitis C (HCV), the most important causes of chronic liver disease and HCC (Kim & Han 2012).

Multiple classification schemes have been suggested for this aggressive disease; the most commonly implemented system has been the Barcelona Clinic Liver Cancer (BCLC) system, which is characterised by integrating disease-related factors as well as patient-related factors (Child-Pugh classification and performance status assessment) in one unified system (Song & Bae 2012). The BCLC classification scheme has been adopted globally and has significantly influenced many national and international guidelines (Park et al. 2013).

Many patients with HCC present with advanced disease (BCLC C) that is not suitable for loco-regional therapies (such as resection, transplantation, radio frequency ablation or transarterial therapies) due to either the high burden of liver disease, extra-hepatic spread or poor performance status related to cirrhosis. Such patients may be candidates for palliative systemic therapies.

Sorafenib, an orally available, multi-tyrosine kinase inhibitor, is the only systemic therapy to demonstrate significant survival benefit over supportive care in the context of two robust randomised controlled trials (Llovet et al. 2008, Cheng et al. 2009). However, a lack of prognostic
Endocrine-Related Cancer

hormone (GH), thyroid-stimulating hormone (TSH), and inhibition of important hormones such as growth hormone (GH), thyroid-stimulating hormone (TSH), and prolactin (PRL). While in the gastrointestinal tract, SST secretion controls gastric acid production and also inhibits the release of other hormones such as gastrin, cholecystokinin, glucagon, secretin, vasoactive intestinal peptide (VIP), gastric inhibitory polypeptide (GIP) and insulin. SST can also decrease gastrointestinal motility and gallbladder contraction by reducing blood flow and inhibit exocrine pancreatic secretion (Lamberts et al. 1996).

Five SSTR subtypes have been characterised: SSTR1, SSTR2, SSTR3, SSTR4 and SSTR5. All SSTRs have capability to bind natural SST14 and SST28 with a high affinity, while there is a significant variation in binding of synthetic SST peptides or somatostatin analogues (SSAs) (Barbieri et al. 2013) (see Table 1).

SSTRs are inhibitory G protein-coupled receptors that are ubiquitously expressed in normal tissues and cancer. They are located in the cellular membrane with seven membrane-spanning domains and are coupled to trans-membrane calcium and potassium ion channels, and intracellular enzymes including adenylate cyclase (ACL) and phosphotyrosine phosphatases (PTPs) such as Src homology phosphatase 1 (SHP1), Src homology phosphatase 2 (SHP2) and phosphotyrosine phosphatase η (PTPη). Upon binding of SST or SSAs, SSTRs activate intracellular pathways that result in anti-secretory effect (Fig. 1A), inhibition of proliferation (Fig. 1B) and apoptosis (Fig. 1C) (Lamberts et al. 1996, Dasgupta 2004, Barbieri et al. 2013). An anti-angiogenic effect of SST and SSAs has also been described, which seems to be related to paracrine inhibition

### Biology of somatostatin and SSTRs

Somatostatin (SST) was first described in 1968 as a hormone secretion inhibitor molecule (Krulich et al. 1968) and was later found to be coded by a unique human gene (SST) on the short arm of chromosome 3. The SST protein has two active forms produced by alternative cleavage of a single pre-protein: one of 14 amino acids (SST14) and the other of 28 amino acids (SST28), which differ in their potency rather than in their function (see Table 1) (Benoit et al. 1990).

Secretion of SST in the hypothalamus results in inhibition of important hormones such as growth hormone (GH), thyroid-stimulating hormone (TSH), and prolactin (PRL). While in the gastrointestinal tract, SST secretion controls gastric acid production and also inhibits the release of other hormones such as gastrin, cholecystokinin, glucagon, secretin, vasoactive intestinal peptide (VIP), gastric inhibitory polypeptide (GIP) and insulin. SST can also decrease gastrointestinal motility and gallbladder contraction by reducing blood flow and inhibit exocrine pancreatic secretion (Lamberts et al. 1996).

Five SSTR subtypes have been characterised: SSTR1, SSTR2, SSTR3, SSTR4 and SSTR5. All SSTRs have capability to bind natural SST14 and SST28 with a high affinity, while there is a significant variation in binding of synthetic SST peptides or somatostatin analogues (SSAs) (Barbieri et al. 2013) (see Table 1).

SSTRs are inhibitory G protein-coupled receptors that are ubiquitously expressed in normal tissues and cancer. They are located in the cellular membrane with seven membrane-spanning domains and are coupled to trans-membrane calcium and potassium ion channels, and intracellular enzymes including adenylate cyclase (ACL) and phosphotyrosine phosphatases (PTPs) such as Src homology phosphatase 1 (SHP1), Src homology phosphatase 2 (SHP2) and phosphotyrosine phosphatase η (PTPη). Upon binding of SST or SSAs, SSTRs activate intracellular pathways that result in anti-secretory effect (Fig. 1A), inhibition of proliferation (Fig. 1B) and apoptosis (Fig. 1C) (Lamberts et al. 1996, Dasgupta 2004, Barbieri et al. 2013). An anti-angiogenic effect of SST and SSAs has also been described, which seems to be related to paracrine inhibition

<table>
<thead>
<tr>
<th>Receptor</th>
<th>SSTR1</th>
<th>SSTR2</th>
<th>SSTR3</th>
<th>SSTR4</th>
<th>SSTR5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expression (non-tumoural tissue)</td>
<td>Brain, lungs, stomach, jejunum, kidneys, liver and pancreas</td>
<td>Brain, jejunum, colon, pancreas (α cells) liver and adrenals (cortex and medulla)</td>
<td>Brain, thyroid and pancreas</td>
<td>Brain and lungs</td>
<td>Brain, heart, adrenal gland, thyroid, placenta, pituitary, small intestine, skeletal muscle and pancreas (β cells)</td>
</tr>
<tr>
<td>Binding affinity by SST14 (IC₅₀ nM)</td>
<td>Yes (0.1–2.26)</td>
<td>Yes (0.2–1.3)</td>
<td>Yes (0.3–1.6)</td>
<td>Yes (0.3–1.8)</td>
<td>Yes (0.2–0.9)</td>
</tr>
<tr>
<td>Binding affinity by SST28 (IC₅₀ nM)</td>
<td>Yes (0.1–2.2)</td>
<td>Yes (0.2–4.1)</td>
<td>Yes (0.3–6.1)</td>
<td>Yes (0.3–7.2)</td>
<td>Yes (0.05–0.4)</td>
</tr>
<tr>
<td>Binding affinity by Octreotide (IC₅₀ nM)</td>
<td>No (&gt; 1000)</td>
<td>Yes (0.4–2.1)</td>
<td>No (4.4–34.5)</td>
<td>No (&gt; 1000)</td>
<td>Yes (5.6–32)</td>
</tr>
<tr>
<td>Binding affinity by Lanreotide (IC₅₀ nM)</td>
<td>No (&gt; 1000)</td>
<td>Yes (0.5–1.8)</td>
<td>No (43–107)</td>
<td>No (&gt; 1000)</td>
<td>Yes (0.6–14)</td>
</tr>
<tr>
<td>Binding affinity by Pasireotide (IC₅₀ nM)</td>
<td>Yes (9.3)</td>
<td>Yes (1)</td>
<td>Yes (1.5)</td>
<td>No (&gt; 100)</td>
<td>Yes (0.16)</td>
</tr>
</tbody>
</table>

IC₅₀ nM: half maximal inhibitory concentration (IC₅₀ represents the concentration of a drug that is required for 50% inhibition in vitro; the lower the IC₅₀, the better the affinity).
of the excretion of pro-angiogenic molecules such as VEGF and insulin growth factor (IGF) via ACL inhibition (Fig. 1A) (Garcia de la Torre et al. 2002, Ristori et al. 2008).

**SSTRs and solid tumours**

During the last two decades, the pro-apoptotic, anti-angiogenic and anti-proliferative effects of SSTR activation (see Fig. 1 for more detail) have been investigated in multiple translational and clinical research studies with the aim of developing new therapeutic options for solid malignancies. The large majority of these studies have failed to show a clinically relevant anti-tumour effect, most probably due to the co-existence of other activated pathways driving oncogenesis (Hejna et al. 2002, Keskin & Yalcin 2013). The best examples of this failure are two randomised phase II trials investigating SSA therapy in patients with advanced breast cancer, both of which reported no benefit in progression-free survival (PFS) (Ingle et al. 1999, Bajetta et al. 2002). Similarly, a phase III randomised study in 260 patients with advanced colorectal cancer did not identify a benefit in survival (neither in time to progression nor in overall survival (OS)) in the SSA arm (Goldberg et al. 1995).

By contrast, an anti-tumour effect of SSA therapy has been demonstrated in advanced neuroendocrine tumours (NETs) in two large randomised studies both reporting significant and clinically relevant benefits: the PROMID (Rinke et al. 2009) and CLARINET (Caplin 2014) trials.

Currently, advanced NETs are the only clinical setting where SSAs can be employed for tumour control outside a clinical trial.

**Figure 1**

Schematic of the SSTR and its downstream activation of secretion and anti-angiogenesis. SSTR, somatostatin receptor; SST, somatostatin; SSAs, somatostatin analogues; Vdc, voltage-dependent channel; Ca$^{2+}$, calcium; K$^+$, potassium; G, G protein; ACL, adenylate cyclase; VEGF, vascular endothelial growth factor; Src, Rous sarcoma oncogene; SHP1, Src homology phosphatase 1; SHP2, Src homology phosphatase 2; PTPh, phosphotyrosine phosphatase; Ras, Raf, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase; AKT, protein kinase B; Zac1, zinc finger protein regulator of apoptosis and cell cycle arrest; p, protein; NF-kB, nuclear factor kappa B; BAX, B-cell lymphoma 2 (BCL2)-associated X protein; JNK, c-Jun N-terminal kinases; ↑, increase; ↓, decrease; /green arrows, activation; /red arrows, inhibition.
Prognostic and predictive values of SSTR expression in HCC

HCCs display differential immunohistochemical (IHC) expression profiles for SSTRs; for example, in a study by Blaker et al. (2004), the overall expression rates of different subtypes (SSTR1, SSTR2, SSTR3, SSTR4 and SSTR5) in 56 specimens obtained from liver resection or transplantation were 46, 41, 64, 0 and 75% respectively. Higher expression of SSTR2 (67%) was shown by Verhoef et al. (2008), who were unable to correlate this expression with any other clinical or molecular characteristics including DNA ploidy status, Ki67 staining and tumour suppressor gene expression such as p16 (CDKN2A), p53 (TP53) and RB1. Moreover, Koc et al. (2013) reported positive expression of SSTR1 and SSTR5 by IHC in, respectively, 76 and 51% of needle biopsy samples from 41 patients diagnosed with HCC. Thus, the available literature indicates variable expression of SSTR subtypes in HCC. This may be related to non-standardisation of the methodology for measurement of SSTRs, differential SSTR expression among different stages of HCC or differences in the molecular biology of different aetiologial and pathological subtypes of HCC. Nevertheless, SSTRs are expressed by a clinically meaningful proportion of HCC and may therefore be potential therapeutic targets.

Consequently, a number of preclinical and clinical studies have evaluated the potential prognostic value of SSTR expression profiles in HCC. For example, in a study by Li et al. (2012), specimens from 76 patients with operable HCC were evaluated. Down-regulation of SSTR transcription was found to result in a loss of a tumour-suppressive mechanism, thus characterisation of SSTR expression may identify a more aggressive disease and hence be a useful prognostic parameter in HCC.

Other studies have evaluated the predictive influence of SSTR expression in HCC patients treated with SSAs. In one study (Liu et al. 2013), expression of SSTR2 and SSTR5 mRNA was evaluated in 99 patients with early-stage hepatitis B virus (HBV)-related HCC who were treated with octreotide LAR following surgery; 47 patients were classified as ‘high expression’ and 52 patients ‘low expression’. The tumour recurrence rate was significantly lower in the high-expression group compared with that of the low-expression group (64 vs 83%; P = 0.033). Additionally, the median disease-free survival was 6.6 years (95% CI 5.2–8.0) in the high-expression group and 3.4 years (95% CI 2.5–4.3) in the low-expression group. Additionally, Borbath et al. (2012) have reported on a case of metastatic HCC with SSTR2 overexpression showing partial regression and more than 3 years of PFS on lanreotide treatment. However, consensus on the value of SSTR expression as a predictive biomarker in HCC has not been reached and needs to be further assessed in prospective studies. Moreover, the prognostic and predictive influences of SSTR expression have not been evaluated in the setting of novel systemic anti-angiogenic therapies such as sorafenib.

Preclinical experience with SSTR-targeted therapeutics in HCC

Multiple preclinical studies, most of them in HCC cell lines, have shown an anti-proliferative effect with both human SST (Chou et al. 1987) and SSAs (Chen et al. 2001 and Liu et al. 2004). In addition, Reynaert et al. (2004) demonstrated a significant reduction in the invasive capabilities in those HCC cell lines (HepG2 and HuH7) that were treated with SSA targeting SSTR1. The anti-proliferative effect of SSA has also been analysed in vivo, mainly with nude mice xenografts. Hua et al. (2005) showed an inhibition of the growth of HCC in mice treated with octreotide, compared with controls, and up-regulation of SSTR2 expression and down-regulation of cMET expression. Mice xenografts have also demonstrated an inhibitory influence of SSAs on metastatic spread potentially related to an anti-angiogenic effect of SSAs (Jia et al. 2009). These preclinical data indicating potential anti-proliferative and anti-metastatic influences of SSAs in HCC supported the initiation of clinical studies in patients with HCC.

Clinical experience with SSTR-targeted therapeutics in HCC

A number of different retrospective and prospective studies have been conducted in the last two decades to evaluate the effects of SSAs, particularly octreotide, in advanced HCC (Table 2). However, the results in the majority of unselected patient populations were discouraging. For example, Barbare et al. reported a phase III study conducted in France evaluating long-acting octreotide vs placebo in 272 patients with HCC who were ineligible for curative treatments or had relapsed following potentially curative therapies. At the time of the final analysis, the median OS was 6.53 months (95% CI 4.8–8.3) for octreotide vs 7.03 months (95% CI 5.43–8.53) for placebo (P = 0.34). No objective responses were achieved in the octreotide group but 33% of patients achieved disease stabilisation for a mean time of 5.5 months (95% CI 1.1–9.9), although there was no significant difference in PFS compared with placebo. Thus, it has been concluded that,
### Table 2  Studies evaluating the use of octreotide-based treatment for advanced hepatocellular carcinoma

<table>
<thead>
<tr>
<th>Study</th>
<th>Geographical region</th>
<th>Phase</th>
<th>Treatment regimen</th>
<th>Number of patients</th>
<th>Median PFS</th>
<th>Median OS</th>
<th>Grade 3–4 toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>i. Randomised studies:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yuen et al. (2002)</td>
<td>China, Hong Kong</td>
<td>II</td>
<td>Octreotide LAR vs placebo</td>
<td>70</td>
<td>NR</td>
<td>1.93 months vs 1.97 months</td>
<td>None reported</td>
</tr>
<tr>
<td>Barbar et al. (2009)</td>
<td>Europe/Western regions</td>
<td>III</td>
<td>Octreotide mono-therapy vs placebo</td>
<td>270</td>
<td>3.3 months vs 3.9 months (P=0.26)</td>
<td>6.5 months vs 7.03 months (P=0.34)</td>
<td>Diarrhoea (0.76 vs 0.75%), and hyperglycaemia (6.85 vs 5.2%)</td>
</tr>
<tr>
<td>Verset et al. (2007)</td>
<td>Italy</td>
<td>III</td>
<td>Octreotide–tamoxifen vs tamoxifen alone</td>
<td>109</td>
<td>NR</td>
<td>3 months vs 6 months</td>
<td>Diarrhoea (1% vs 0%) and nausea (0% vs 1%)</td>
</tr>
<tr>
<td>Treiber et al. (2007)</td>
<td>Germany</td>
<td>II</td>
<td>Octreotide–rofecoxib vs octreotide</td>
<td>71</td>
<td>Time to progression (94 days) similar for both arms</td>
<td>Median overall survival (154 days) similar for both arms</td>
<td>None reported</td>
</tr>
<tr>
<td>Becker et al. (2007)</td>
<td>Germany</td>
<td>III</td>
<td>Octreotide LAR vs placebo</td>
<td>120</td>
<td>NR</td>
<td>4.7 months vs 5.3 months</td>
<td>Bleeding (10% vs 8%) and hyperbilirubinaemia (2% vs 2%)</td>
</tr>
<tr>
<td>Kouroumalis et al. (1998)</td>
<td>Greece</td>
<td>II</td>
<td>S.c. octreotide vs no treatment</td>
<td>58</td>
<td>NR</td>
<td>(13 months vs 4 months, P=0.002)</td>
<td>NR</td>
</tr>
<tr>
<td>Dimitroulopoulos et al. (2007)</td>
<td>Greece</td>
<td>II</td>
<td>Octreotide or placebo</td>
<td>127</td>
<td>NR</td>
<td>12 months vs 7.7 months</td>
<td>NR</td>
</tr>
<tr>
<td>ii. Non randomised studies:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shah et al. (2009)</td>
<td>USA</td>
<td>II</td>
<td>Octreotide monotherapy</td>
<td>22 patients</td>
<td>3 months (95% CI 1.7–5.7)</td>
<td>4.5 months (95% CI 2.3–8)</td>
<td>Hypoglycaemia (3.33%), elevation in transaminases or bilirubin (6.67%), and abdominal pain/ cramping (6.67%)</td>
</tr>
<tr>
<td>Prete et al. (2010)</td>
<td>Belgium</td>
<td>II</td>
<td>Sorafenib plus octreotide</td>
<td>50 patients</td>
<td>7 months</td>
<td>12 months</td>
<td>Diarrhoea (6%) and hypertension (4%)</td>
</tr>
<tr>
<td>Schoniger-Hekele et al. (2009)</td>
<td>Austria</td>
<td>Retrospective</td>
<td>Octreotide mono-therapy</td>
<td>95 patients</td>
<td>NR</td>
<td>BCLC A: 31.4 months</td>
<td>NR</td>
</tr>
<tr>
<td>Plentz et al. (2005)</td>
<td>Germany</td>
<td>II</td>
<td>Octreotide or lanreotide (1:1)</td>
<td>41 patients</td>
<td>NR</td>
<td>BCLC B: 22 months</td>
<td>NR</td>
</tr>
<tr>
<td>Raderer et al. (2000)</td>
<td>Austria</td>
<td>II</td>
<td>Octreotide or lanreotide (1:1)</td>
<td>21 patients</td>
<td>2.5 months</td>
<td>4.3 months</td>
<td>NR</td>
</tr>
<tr>
<td>Samonakis et al. (2002)</td>
<td>Greece</td>
<td>Retrospective</td>
<td>Octreotide or lanreotide (1:1)</td>
<td>32 patients</td>
<td>NR</td>
<td>15 months</td>
<td>NR</td>
</tr>
</tbody>
</table>
despite the favourable safety profile, octreotide had limited efficacy in patients with advanced HCC and led to no survival benefit. However, there were no data concerning SSTR expression and survival in this study.

Another phase III study conducted in Belgium evaluated the efficacy of tamoxifen (TMX) alone or in combination with long-acting release octreotide in 109 patients with advanced HCC. The median survival was 3 months (95% CI 1.4–4.6) for patients receiving combination therapy and 6 months (95% CI 2–10) for those receiving TMX alone (P=0.609). There was no difference in terms of a-fetoprotein (α-FP) decrease, tumour regression, improvement of quality of life or prevention of variceal bleeding between the two groups (Verset et al. 2007).

A multicentre phase II study evaluating the combination of sorafenib plus octreotide in advanced HCC (the So.LAR study) has been conducted in Italy; 50 patients with advanced HCC and Child-Pugh score A or B were included and administered sorafenib 800 mg/day for 28 days with a following week of rest and long-acting octreotide at a dose of 40 mg administered every 28 days. Out of 50 patients, 16 (34%) were treatment naïve, while all others had previously received local and/or systemic treatments. Five partial responses were noted (10%), 33 patients had stable disease (66%) and 12 patients disease progression (24%). The median time to progression was 7.0 months (95% CI 3.0–10.9 months), and the median OS was 12 months (95% CI 6.3–17.4 months). Treatment was well tolerated; diarrhoea (6%) and hypertension (4%) were the most frequent grade 3 toxicities (Prete et al. 2010).

The use of SSAs in advanced HCC has been evaluated in a meta-analysis conducted by Ji et al.: 11 randomised controlled trials including 802 patients were assessed and nine studies were included in the meta-analysis. The control group for studies included in the analysis was supportive care in seven studies and placebo in four studies. A pooled analysis of the four trials performed in Western countries indicated no significant differences in 6-month, 12-month, or 24-month OS rates between the octreotide group and the control group (6-month, relative risk (RR) 1.27, 95% CI 1.06–1.52, P=0.09; 12-month, RR 1.69, 95% CI 0.74–3.87, P=0.22; 24-month, RR 0.60, 95% CI 0.33–1.10, P=0.10). While the pooled analysis of five trials conducted in China indicated a significant increase in 6-month and 12-month survival in octreotide-treated patients compared with controls (6-month, RR 1.78, 95% CI 1.25–2.52, P=0.001; 12-month, RR 4.59, 95% CI 1.99–10.59, P=0.0003). The 24-month survival rate was also higher in the octreotide group, but the difference was not significant (RR 7.32, 95% CI 0.92–58.14, P=0.06) (Ji et al. 2011). This suggests that octreotide may prolong survival in patients with advanced HCC, although the effect appears to be limited to non-Western populations. The predictive role of SSTR expression was not investigated in this meta-analysis, as it was reported only in one study (Dimitroulopoulos et al. 2007) and needs to be addressed in future studies as discussed earlier.

In a different setting, Jia et al. evaluated in a non-randomised study whether post-transcatheter arterial chemoembolisation (TACE) combination therapy with unfractionated heparin (1250–2500 U) and octreotide influences development of extrahepatic disease. A total of 147 patients diagnosed with HCC suitable for TACE were enrolled, received 2–4 TACE procedures, and were monitored for 1 year. Of these, 84 received the heparin plus octreotide combination treatment and 63 patients received heparin alone (control group). They found a significant decrease in the incidence of tumour metastasis in patients receiving the combination treatment post-TACE with no significant toxic or adverse effects (Jia et al. 2012); however, the non-randomised nature of this study limits the conclusions that can be drawn. Once again, SSTR expression was not evaluated.

In conclusion, the available data concerning SSAs for tumour control in advanced HCC are insufficient to draw firm evidence-based conclusions and further evaluation of this issue seems to be of value. Moreover, the role of SSAs in HCC subsets such as those with high SSTR expression warrants investigation in prospective studies.

**Novel approaches for optimising SSTR targeting in HCC**

**Pretreatment assessment of SSTRs through nuclear medicine studies**

Two studies have demonstrated the feasibility of scintigraphy to detect SSTRs in advanced HCC using either ${ }^{68}$Ga-DOTATOC PET (Freesmeyer et al. 2009) or (99m)Tc-HYNIC-Tyr(3)-octreotide in human HCC-bearing nude mice (Li et al. 2005). Additionally, in a multicentre French study, the feasibility of SSTR screening using ${ }^{111}$indium pentetreotide in advanced HCC before SSA treatment was evaluated. This study demonstrated SSTR scintigraphic uptake in 36% of primary tumours and 41% of metastatic sites (Nguyen-Khac et al. 2009).

Dimitroulopoulos et al. conducted a randomised controlled trial evaluating long-acting octreotide monotherapy in the treatment of patients with advanced HCC and scintigraphic evidence of ${ }^{111}$indium octreotide accumulation. In this study, a total of 127 cirrhotic patients, stages...
A–B, due to chronic viral infections and with advanced HCC, were enrolled. Scintigraphy with $^{111}$indium-labelled octreotide was performed in all cases. Patients with increased isotope accumulation were randomised to receive either oral placebo only or octreotide/octreotide LAR only as follows: octreotide 0.5 mg s.c. every 8 h for 6 weeks; octreotide LAR 20 mg i.m. at the end of weeks 4–8 and octreotide LAR 30 mg i.m. at the end of week 12 and every 4 weeks, with monthly follow-up and estimation of the quality of life (using the QLQ-C30 questionnaire). Patients with negative SSTR detection were followed up in the same manner. Scintigraphy demonstrated the presence of SSTRs in 61 patients. Thirty were randomised to receive only placebo and 31 only octreotide. A significantly higher survival time was observed for the octreotide-treated group (49 ± 6 weeks) compared with the control group (28 ± 1 weeks) and to the SSTR-negative group (28 ± 2 weeks), $P < 0.01$ (Dimitroulopoulos et al. 2007).

However, the published data with regard to the use of scintigraphy as a prognostic marker in HCC patients treated with SSAs or to predict the benefit from SSA therapy are not consistent. For example, in a study conducted in 63 advanced HCC patients treated with long-acting octreotide, positive scintigraphy was noted in 34 (56%) patients, but there was no relationship with tumour response or the quality of life (Cebon et al. 2006). This discrepancy in the predictive value of octreotide scintigraphy to guide therapeutic decision making needs to be further evaluated in larger randomised prospective controlled studies.

Assessment of predictive serum and tissue biomarkers in patients receiving SSAs

Montella et al. have evaluated the predictive role of VEGF in a cohort of HCC patients receiving octreotide monotherapy. They found a statistically significant positive correlation between increases in serum VEGF levels during octreotide therapy and tumour progression (Montella et al. 2008).

Optimising drug delivery of SSAs

Zhang et al. have evaluated the treatment of liver cancer in mice by the intratumoural injection of an octreotide-based temperature-sensitive gel (OCT-P407). Tumours were injected with OCT-P407 or standard octreotide solution and intratumoural octreotide levels were subsequently measured by HPLC over a specific time period. OCT-P407 maintained an effective intratumoural octreotide concentration for a longer period than standard octreotide and hence may potentially deliver a greater therapeutic effect, although the feasibility of intratumoral drug delivery in humans is unclear (Zhang et al. 2014).

Ongoing studies

Two ongoing clinical trials are investigating therapy with SSAs in HCC patients (www.clinicaltrials.gov; last accessed 1st June 2014). Both studies are targeting unselected population with respect to SSTR expression.

- Phase II trial of pasireotide (an SSA with a broader and more potent affinity, starting at a dose of 60 mg via i.m. injection, every 28 days) in patients with unresectable HCC (after progression with sorafenib) (NCT01639352). This trial is currently recruiting patients (planned sample size: 30 patients). The primary end point is disease control rate (complete response, partial response or stable disease). Secondary outcomes will include PFS, OS, response rate (complete or partial) and duration of response and adverse events.

- Another phase II trial, also with pasireotide (60 mg administered by i.m. injection once in 28 days) and with everolimus (an orally available mTOR inhibitor) (7.5 mg administered daily for 28 days), in patients with advanced or metastatic HCC (NCT01488487) intolerant to systemic treatment with sorafenib. This trial has completed recruitment ($n = 30$). The primary end point is time to progression based on modified HCC RECIST criteria (radiological progression in a previously embolised lobe, development of new lesions in an untreated lobe or evidence of extrahepatic progression). Secondary outcomes will include toxicity, OS and response rate (complete or partial).

Data from these studies will provide the efficacy for patients with advanced HCC; however, the role of SSTR expression and appropriateness for using this as a biomarker predictive of response remain unanswered.

Conclusions and future directions

SSTRs have been extensively studied in preclinical and clinical settings of HCC. With the development of different SSTR-targeted agents, SSTR expression became relevant in terms of anti-tumour efficacy prompting clinical investigation of SSAs in advanced HCC. The available data concerning SSAs for tumour control in advanced HCC are insufficient to draw firm evidence-based conclusions, and further evaluation of this issue seems to be of value. The use of potential biomarkers, including SSTR expression profiling by IHC and scintigraphy, to...
select patients for SSA-based therapy is supported by some preclinical and clinical data, but needs to be further investigated in large prospective studies.

The highly varied aetiology and natural history of HCC implies a similarly heterogeneous array of molecular genetic abnormalities. The development of a robust molecular classification system to define the more common aberrations in HCC should present new potential biomarkers and opportunities for personalisation of therapy in HCC, and it seems likely that SSTRs may have a role to play in this process.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

Funding
This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

References


