Review

Is There a Place for Somatostatin Analogues for the Systemic Treatment of Hepatocellular Carcinoma in the Immunotherapy Era?

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Abstract: Patients with advanced hepatocellular carcinoma (HCC) have a very limited survival rate even after the recent inclusion of kinase inhibitors or immune checkpoint inhibitors in the therapeutic armamentarium. A significant problem with the current proposed therapies is the considerable cost of treatment that may be a serious obstacle in low- and middle-income countries. Implementation of somatostatin analogues (SSAs) has the potential to overcome this obstacle, but due to some negative studies their extensive evaluation came to a halt. However, experimental evidence, both in vitro and in vivo, has revealed various mechanisms of the anti-tumor effects of these analogues, including inhibition of cancer cell proliferation and angiogenesis and induction of apoptosis. Favorable indirect effects such as inhibition of liver inflammation and fibrosis and influence on macrophage-mediated innate immunity have also been noted and are presented in this review. Furthermore, the clinical application of SSAs is both presented and compared with clinical trials of kinase and immune checkpoint inhibitors (ICIs). No direct trials have been performed to compare survival in the same cohort of patients, but the cost of treatment with SSAs is a fraction compared to the other modalities and with significantly less serious side effects. As in immunotherapy, patients with viral HCC (excluding alcoholics), as well as Barcelona stage B or C and Child A patients, are the best candidates, since they usually have a survival prospect of at least 6 months, necessary for optimum results. Reasons for treatment failures are also discussed and further research is proposed.

Keywords: advanced hepatocellular carcinoma; somatostatin analogues; HCC immunotherapy; patient selection

1. Introduction

Primary liver cancer is the seventh most prevalent cancer and the fourth cause of cancer-related deaths worldwide [1].

Deaths from hepatocellular carcinoma are rising faster than deaths from any other type of cancer in the United States [2]. Current treatment of advanced HCC is rather disappointing, as its benefits in terms of survival are measured in months rather than years even after introduction of multi-kinase inhibitors and immunotherapy [3].

The HCC world incidence varies. It usually-but not always-follows the prevalence of viral hepatitis either B or C. China, Eastern Asia and Africa report the highest HCC rates, with the lowest figures in Northern Europe and the USA. Eastern European and Mediterranean countries show intermediate figures [4].
The greatest obstacle in setting up a therapeutic trial or in comparing the results of different trials is the heterogeneity of HCC together with the fact that in most instances (over 80%) there are two diseases (cirrhosis and cancer), each affecting the natural course of the other. To overcome this problem, many classifications have been proposed. The most extensively used, but by no means perfect, is the Barcelona Clinic Liver Cancer (BCLC) staging. HCC is classified into very early stage (BCLC stage 0), early stage (BCLC A), intermediate stage (BCLC B), advanced stage (BCLC C) and terminal stage (BCLC D) [3].

The use of deep genome sequencing, transcriptome, epigenome, proteome and single-cell analysis tests started to unveil tumor heterogeneity, which may lead to a change in the classification of HCC. These technological changes are important not only for immunotherapy but also for re-evaluation of previous treatments [5].

Kinase inhibitors and immune checkpoint inhibitors (ICI) were recently introduced as systemic treatment of HCC. Favorable results showed promising efficacy in early-phase trials with single agents, but this was not confirmed in phase III trials. The combination of atezolizumab (an anti-PD-L1 ICI) with bevacizumab (an anti-VEGF antibody) was accepted as first-line therapy in 2020, but again the results are still not that impressive [6].

Soon after its discovery in 1968, somatostatin (SST) was shown to have many potential therapeutic implications and a host of synthetic somatostatin analogues (SSAs) with longer half-lives (i.e., octreotide, vapreotide, lanreotide and pasireotide) available for clinical use ensued [7].

We summarize the current place of SSAs in the era of kinase and immune checkpoint inhibitors (ICIs) based on two important recent observations: (1) depending on HCC etiology, different results were noted. ICIs performed the worst in NAFLD-associated HCC and the best in viral-associated HCC. (2) The best results were seen in Child Pugh A patients and the B and C stages of the BCLC classification.

2. Mechanisms of SSAs’ Activity in HCC

Experimental data have provided convincing evidence that SSAs have a beneficial effect on HCC. Binding of SST and SSAs to their respective receptors activates various intracellular pathways leading to several antineoplastic effects through cell proliferation, apoptosis and possibly autophagy [8]. Data on SST receptor expression in both hepatocytes and liver sinusoidal cells and a detailed review of the antineoplastic mechanisms have recently been published [9].

Results on cellular proliferation are not uniform. Most studies indicate that octreotide induces cell cycle arrest. This process is regulated by the presence of specific SSTR subtypes [10,11] as well as the concentration of the peptide and the time of exposure. Thus, the administration of SSAs had a dual effect: low concentrations reduced proliferation while higher concentrations increased proliferation [12]. In Hepatoblastoma G2 (HepG2) cells, inhibition of proliferation was obtained at a concentration of $10^{-8}$ mol/L [13]. Short-term octreotide treatment could lead to SSTR2 desensitization and reduced HCC response. However, long-term octreotide administration inhibited the growth of HCC effectively—possibly through the re-sensitization and upregulation of SSTR2 [14].

The anti-tumoral action of SSAs is further mediated through the enhancement of apoptosis [12–14].

Autophagy is a double-edged sword in hepatocellular carcinoma and may either be protective or detrimental [15]. In normal cells and at the initial stages of HCC, autophagy is a tumor suppressor and maintains genomic stability. However, once HCC is established, autophagy will promote cell survival and tumor growth [16]. The effects of SSAs on autophagy are very few. Octreotide increased autophagy markers and hepatoprotection in a rat model of ischemia-reperfusion liver injury [17].

Additional mechanisms of the anti-tumor effect of SSAs have been proposed. They suppress several trophic factors implicated in the migration and tumor progression, such as insulin-like growth factors 1 and 2 (IGF1 and IGF2) [18]. Other potential tumor trophic
factors such as gastrin, glucagon and insulin are also inhibited by SSAs, but their exact role in HCC has not been clarified yet [19].

HCC-induced angiogenesis is also inhibited by octreotide [20], either through direct binding to the endothelium or indirectly through the inhibition of the vascular endothelial growth factor (VEGF) [21,22]. This is particularly important, as a combination of SSAs with a multi-kinase inhibitor seems therapeutically rational.

Modification of innate immunity response is an additional antineoplastic mechanism [23]. Octreotide pre-incubation of Kupffer cells inhibited tumor necrosis factor a (TNFa) and nitric oxide (NO) secretion, but it also reduced the production of the pro-inflammatory cytokine interleukin-12 (IL-12), whereas the anti-inflammatory IL-13 secretion was increased [24]. HCC, like most neoplasms, is associated with inflammation; therefore, reduction in inflammation may be an indirect antineoplastic mechanism.

Liver and tumor-associated macrophages (TAMs) are also implicated in HCC progression. At the initial stages of HCC, Kupffer cells and TAMs overproduce transforming growth factor beta 1 (TGFb1) and IL-6, favoring a tumor-promoting M2 macrophage polarization [25]. Octreotide inhibited the production of TGFb1 by isolated Kupffer cells [26]. It is conceivable then that M2 polarization will also be reduced. In addition, a reduction in the apoptosis of cultured Kupffer cells incubated with octreotide has been described which may strengthen the defense against HCC [27].

Most HCCs develop in a cirrhotic background, and octreotide has effectively attenuated liver fibrosis in a rat fibrosis model [28]. The CCL2 (monocyte chemoattractant protein-1 or MCP-1) chemokine is also implicated in the process of liver fibrosis [29]. Stimulation of Kupffer cells with lipopolysaccharide (LPS) led to the production of significantly increased amounts of both CC chemokines (MCP-1, Rantes) and CXC chemokines (IL-8, macrophage inflammatory protein-2 or MIP-2). Octreotide considerably reduced CC chemokines but not CXC chemokine production [30]. Moreover, octreotide, synergistically with LPS, stimulated the production of increased amounts of collagenase (MMP1) by Kupffer cells and decreased several pro-fibrotic factors in unstimulated Kupffer cells, including TGFb. Both these effects eventually led to attenuation of liver fibrosis [26].

Apart from Kupffer cells, hepatic stellate cells (HSCs) are also involved in liver fibrosis by producing the components of extracellular matrix. HSCs permit tumor growth by producing hepatocyte growth factor [31]. Somatostatin had no effect on HSCs proliferation but significantly inhibited collagen production and strongly repressed platelet-derived growth factor (PDGF) and TGFb1-dependent procollagen production [32,33], thus attenuating fibrosis (Figure 1).

HSCs are implicated in the development of inflammation even though they do not belong to the innate immune system, as they produce several pro-inflammatory molecules [34]. Secretion of the pro-inflammatory cytokines IL-1beta and IL-8 by rat HSCs is inhibited by somatostatin [35,36].

Animal models add further support to the antineoplastic effects of SSAs in HCC. Octreotide inhibited HCC development after implantation of Morris hepatoma cells [37]. Studies from China in the nude mice model of HCC showed that tumor growth and lung metastases were decreased after octreotide administration and survival was considerably prolonged [38]. The combination of an SSA with a cyclooxygenase (COX 2) inhibitor suppressed the metastasis of HCC in nude mice [39]. The long-acting lanreotide was effective in chemically-induced HCCs, inhibiting cell proliferation and reducing angiogenic factor levels, while apoptosis was increased [40].
In view of the above preclinical data, it was only logical that SSAs were tested in clinical studies for the treatment of HCC.

3. Somatostatin Analogues as a Systemic Treatment of HCC

3.1. Positive Studies (Table 1)

Subcutaneous octreotide was initially used in a randomized controlled study of Okuda II and III HCC cirrhotic patients. Survival rates almost doubled and there was a significant reduction in the risk of death. These results were confirmed with long-acting analogues in a non-randomized trial where the relative risk of death of the control patients was 2.7 higher. Interestingly, 10% of tumors regressed and 30% were stable, a result closely approaching the expression of SSTRs reported before. Despite radiologic progression of tumors, patients had no significant weight loss and retained their appetite. HCC and cirrhosis in both trials were due to either HBV or HCV in approximately 90% of cases [41,42]. The somatostatin survival benefit became apparent in the Kaplan–Meier curves only after 6 months of treatment. The worst response was observed in alcoholic cirrhosis, particularly in active drinkers [43].

Lanreotide also showed a 43% response rate, in an uncontrolled study. It should be noted that octreotide scintigraphy was negative for receptor expression in all patients; 24% of patients had a significant reduction in serum-a fetoprotein (AFP) levels [44].

Two additional studies from other Greek centers also demonstrated favorable results. The first, with viral hepatitis HCC cases, showed prolonged survival only in non-cirrhotic patients. However, 40% of their cirrhotics were Child Pugh C and many died before the critical time of 6 months [45].

A second randomized controlled study of viral-related hepatitis patients also demonstrated that octreotide doubled the survival of those with detectable SSTRs on 111 Indium
octreotide scintigraphy. No survival benefit was observed in SSTR-negative patients and again, the benefit was significant after approximately 6 months of therapy [46].

Twenty patients with advanced HCC were treated with octreotide LAR, while forty patients with comparable staging and liver function were retrospectively selected as controls. Results were published as an abstract. The treated patients not only had a significant survival gain compared to controls but also exhibited significant correlation with SSTR2 expression in the tumor [47].

Tamoxifen and octreotide in combination were used in a controlled trial from China. Survival was doubled compared to conventional chemotherapy with a response rate of 43% in the octreotide arm [48].

A Pakistani controlled trial showed regression of HCC in 45.4% of patients with significant survival benefit and improved quality of life. A parallel decrease in a-fetoprotein in 50% of patients was also observed [49].

A small observational study of advanced HCC from the USA reported a median survival of only 4.5 months. Yet, 27% of their patients lived for more than 10 months. Those were patients of Asian descent infected with the Hepatitis B virus [50].

Total regression of HCC after SSA treatment was shown in a patient with viral cirrhosis [51]. An additional case report presented a patient with HBV-related HCC and lung and mediastinal metastases. Treatment with lanreotide reduced the mediastinal nodes considerably, while the lung nodes regressed completely. Remission lasted for 42 months. SSTR2 overexpression was identified in tumor tissue [52].

The importance of SSTR2 and SSTR5 expression was clearly demonstrated in two large Chinese studies of operable early-stage liver tumors after the surgical removal of HCC. In the first trial [53], patients were divided and treated according to the presence or absence of SSTRs in the tumor tissue. Survival was significantly longer if receptors were present. Similarly, in the second study of HBV-associated HCC, patients survived longer when a high expression of SSTR2 was present [54].

SSAs have been directly compared to transarterial chemoembolization (TACE) and radiofrequency ablation (RAF). Non-randomly selected patients were treated with octreotide and a group of TACE-treated patients served as the control in a German trial. The survival of approximately 19 months was similar in both groups [55]. A larger randomized trial from the same country confirmed these results. Schoniger-Hekele et al. retrospectively studied 95 BCLC stage A and B, matched HCC patients given octreotide, TACE, multimodal therapy or only palliative care. Median survival was similar in all treatment modalities and significantly higher than palliative treatment. Results were similar irrespective of the BCLC stage [56].

In a slightly different trial, 147 HCC non-randomized patients were treated with 2–4 TACE applications. One group received heparin and octreotide as an adjunct therapy and was compared with heparin-only controls. After a one-year follow-up there was a statistically significant lower incidence of metastatic tumors in the octreotide group [57].

In a similarly designed Chinese study, patients with BCLC stages B or C were randomly assigned to be treated with either TACE or TACE plus celecoxib and octreotide. After 3 years of follow-up, a median survival of 15 months was reported in the combination group: two times higher than the 7.5 months of the TACE-only group. The survival benefit was very significant for both BCLC stage B and C. Quality of life was improved in the octreotide group, where the incidence of the post-embolization syndrome was significantly lower. It should be noted that most patients were infected with either HBV or HCV [58].

RAF followed by octreotide was used in an observational study of Child A and Child B patients with viral cirrhosis with multiple liver HCC nodules. Mean survival was 31.4 months; 80% of patients had a clinical response while 14% had complete or partial tumor regression associated with serum VEGF levels [59].

A study of pasireotide in advanced HCC of viral etiology was recently published. The best response was stable disease in nine patients (45%). Median time to tumor
progression was 3 months, and median survival was 9 months, even though 75% had BCLC stage C and 55% had metastatic disease. It should be noted that all patients were treatment failures: 60% had prior TACE treatment and 70% had received sorafenib before [60].

Table 1. Summary of the positive studies about the role of somatostatin analogues in the treatment of advanced HCC.

| Authors                          | Type of Study | No. of Patients | SST Receptors Assessment | Intervention | Control | Outcomes                                                                                                                                 |
|----------------------------------|---------------|-----------------|---------------------------|--------------|---------|------------------------------------------------------------------------------------------------------------------------------------------|
| Kouroumalis E et al., 1998 [41]  | RCT           | 58 patients with advanced HCC | Histology in all cases | Octreotide 250 μg s.c. b.i.d in 28 patients | No treatment in 30 patients | • Increased median survival (13 mos. vs 4 mos.) in the treated group  
• Increased cumulative survival rate at 6 mos. (75% vs 37%) and 12 mos. (56% vs 13%) in the treated group |
| Samonakis DN et al., 2002 [42]  | Comparative observational study | 59 patients with inoperable HCC | N/A | Long-acting somatostatin analogues in 32 patients | No treatment in 27 patients | • Improved OS in the treated group (15 mos. vs 8 mos.)  
• HCC remained stable or regressed in 40% of the treated patients |
| Raderer M et al., 2000 [44]      | Uncontrolled study | 21 patients with inoperable HCC | Scintigraphy in 15 patients | Lanreotide 30 mg i.m. every 14 days | None | • 24% had a decrease in serum AFP levels by 30%  
• 5% showed a partial response to treatment  
• 38% had stable disease |
| Patsanas T et al., 2004 [45]      | Comparative observational study | 30 patients with unresectable HCC (group A: cirrhosis group B: non-cirrhosis) | N/A | Octreotide 500 μg s.c. b.i.d | None | • Octreotide improved significantly the survival time in non-cirrhotic patients with HCC compared to cirrhotic patients (mean survival time 8.3 mos. vs 5 mos.)  
• Octreotide administration stopped gradual elevation of serum AFP levels |
| Dimitroulopoulos D et al., 2007 [46] | RCT | 127 cirrhotic patients, stages A–B, due to chronic viral infections with advanced HCC, 61 patients with positive SSTR were | Scintigraphy in all cases | Oral placebo in 30 patients | 31 patients with SSTR positive were treated with octreotide 0.5 mg s.c. every 8 h for 6 wk., at the end of wk. 4-8 octreotide LAR 20 mg i.m. and at the end of wk. 12 and | • A significantly higher survival time was observed for the octreotide group (49+/−6 wk.) as compared to the control group (28+/−1 wk.) and to the SSTR negative group (28+/−2 wk.) |
| Study | Design | Patients | Study Details | Results |
|-------|--------|----------|---------------|---------|
| Pan DY et al., 2003 [48] | RCT | 39 patients with inoperable HCC | 24 patients were treated with TAM + OCT | 15 patients were treated with regular chemotherapy: TAM + OCT group lowered AFP levels, TAM + OCT increased median survival compared to chemotherapy (12.8 mos vs 5.5 mos.) |
| Gill ML et al., 2005 [49] | Comparative observational study | 42 patients with inoperable HCC | 22 patients were treated with long-acting octreotide 100mcg s.c. t.i.d for 2 wks. followed by 20mg i.m. monthly | 20 patients with no treatment due to socioeconomic issues: Tumor size regression in 45.5% of the patients treated, Decrease of serum AFP levels in 50% of the patients treated, Octreotide LAR increased survival in 6 mos. follow up compared to no treatment group (64% vs 50%) |
| Shah U et al., 2009 [50] | Observational study | 22 patients with advanced HCC and CLIP score of 3 or higher | 22 patients were treated with long-acting octreotide 30 mg i.m. (or 20 mg) monthly | Treatment with long-acting octreotide showed: Median TTP of 5.7 mos., Median PFS time of 3 mos., Median OS time of 4.5 mos., 6 out of 22 patients achieved an OS time of greater than 10 mos. |
| Siveke JT et al., 2003 [51] | Case report | 1 patient with advanced HCC | Octreotide 250 μg b.i.d followed by long-acting octreotide 10mg monthly | Tumor size reduction by 50–70% after 4 mos., Complete tumor regression after 10 mos. |
| Borbath I et al., 2012 [52] | Case report | 1 patient with metastatic HCC | Lanreotide 30 mg twice monthly | Tumor size regression and remission for 42 mos. |
| Li S et al., 2012 [53] | Observational study | 76 patients with inoperable HCC | Octreotide | Mean survival time was longer in the high SSTR-2/5 expression group |
| Authors            | Type of Study | Patients | Observational Study | Tumor Tissue | Treatment | Results |
|--------------------|---------------|----------|---------------------|--------------|-----------|---------|
| Liu Y et al., 2013 [54] | Observational study | 99 patients with HCC and cirrhosis who underwent curative liver resection | Histology | Octreotide LAR i.m. monthly for 12 mos. | Tumor recurrence rate was significantly lower in the high expression group compared with that of the low expression group (63.83% vs. 82.69%) |
| Plentz RR et al., 2005 [55] | Observational study | 41 patients with advanced HCC and cirrhosis | N/A | Octreotide 250 μg t.i.d followed by long-acting octreotide 30 mg i.m. monthly | Tumor size was stable in 63% of the patients treated after a median follow-up of 21 mos. |
| Schöniger-Hekele M et al., 2009 [56] | Retrospective observational study | 95 patients with HCC (BCLC stage A or B) | N/A | Octreotide TACE, multimodal therapy, palliative care | Survival under octreotide treatment was not different compared to TACE or multimodal therapy |
| Jia W et al., 2012 [57] | RCT | 147 patients with HCC receiving 2–4 TACE treatments | N/A | Octreotide 84 patients were treated with heparin + octreotide for 12 mos. | A significant decrease in the incidence of tumor metastasis in patients receiving the combination treatment post-TACE for up to 1 year with no significant toxic or adverse effects |
| Tong H et al., 2017 [58] | RCT | 71 patients with inoperable HCC | N/A | Octreotide 36 patients were treated with TACE + C + L | During a 3-year follow-up period: |
|                     |               |          |                     | 35 patients were treated with TACE | Disease control rate of the TACE + C + L group was significantly higher than that of the TACE group either at 6 mos. (72.2% vs 42.9%) or at 12 mos. (61.1% vs 28.6%) |
Montella L et al., 2008

Observational study

35 patients with advanced HCC and Child A or B cirrhosis

N/A

35 patients treated with RFA + octreotide

None

- Mean OS was 31.4 mos.
- 80% of the patients had a clinical response
- 14.2% of the patients had complete or partial tumor regression associated with serum VEGF levels

Feun LG et al., 2018

Observational study

20 patients with advanced or metastatic HCC (BCLC stage C or D)

N/A

20 patients were treated with pasireotide LAR 60mg i.m. monthly

None

- 45% of the patients had stable disease
- Median TTP was 3 mos.
- Median survival was 9 mos.
- 90% of the patients had prior therapy that failed

Abbrev.: RCT, randomized controlled trial; HCC, hepatocellular carcinoma; s.c., subcutaneous; i.m., intramuscular; b.i.d., twice a day; mo(s), month(s); N/A, not applicable; OS, overall survival; AFP, α-fetoprotein; SSTR, somatostatin receptors; wk(s), week(s); TAM, tamoxifen; OCT, octreotide; t.i.d., three times a day; TTP, time to tumor progression; PFS, progression free survival; TACE, transarterial chemoembolization; C, celecoxib; L, lanreotide; RFA, radiofrequency ablation.

3.2. Negative Studies (Table 2)

There have been several negative studies that demonstrate no survival benefit from the administration of SSAs. One is a retrospective observational study of 63 patients, almost half of which also presented alcoholic cirrhosis [61]. Yuen et al. published a randomized trial with no survival benefit [62]. This study has been criticized by us and many others due to the extremely low median survival of 1.9 months of the controls compared to only 2 months in the long-acting SSA group, suggesting that most patients were obviously moribund, as they received only one octreotide injection [63].

It should be noted that the BCLC new stratification advocates that systemic treatment should be given only at stages B and C but not D (primarily moribund patients with expected survival of up to 3 months), further disproving the value of most negative SSA trials which mainly focused on BCLC D patients [64].

A limited survival benefit of octreotide treatment was also reported by a non-randomized study [65]. Again, 6% of cases had a short survival due to the rapid progression of the disease, so in fact they had received no treatment, but they were nevertheless analyzed in the final report. An additional 56% received four doses or less, likely indicating that their stage was also BCLC D. Even so, 50% of patients who were treated for at least three months were considered to be stable, in agreement with previous studies [63,66].

An open trial (with 22% alcoholic cirrhosis patients) showed a small anti-tumor effect of SSAs with a median survival of 8 months. However, treatment was discontinued not because of death but because of either toxicity or disease progress. Therefore, actual survival could not really be assessed [67].

Another open-label trial (88% BCLC stage C and more than 60% alcoholics) reported a median survival of only 6.7 months. The same problems were evident, as treatment stopped not because of death but rather because of disease progression. It is further noteworthy that only a median of two 28-day cycles was administered [68].
A randomized controlled study compared treatment with tamoxifen plus octreotide against a control group that received only tamoxifen: 52.4% of the patients were alcoholics. No survival gain was demonstrated for the tamoxifen plus octreotide group. Yet again, combination patients survived for a median of only 3 months and almost half of them received one to three injections. In addition, Child Pugh A patients had a very low median survival of only 6 months [69].

A double-blind, placebo-controlled study (HECTOR) also reported no survival gain for octreotide (median survival of 4.7 months compared to 5.3 months of the controls) without an effect on quality of life: 52% of the treatment group had alcoholic cirrhosis and only 40% survived for the critical 6-month period [70].

Another multicenter randomized placebo-controlled study also reported negative results. Again, almost 50% of the participating patients suffered from alcoholic cirrhosis [71].

A Chinese meta-analysis of nine studies with almost 800 patients may possibly explain the conflicting results. The survival gain was clearly in favor of octreotide treatment during a 6- and 12-month follow-up. Interestingly, the survival gain was not significant when only Western studies were included [72]. This report clearly demonstrates a discordance between China (and Greece) and the West.

There are many potential explanations for the negative results from primarily Western studies. The desensitization of SST receptors after short exposure to octreotide may be one of them, but if researchers had persevered, there is evidence that re-sensitization may occur after prolonged administration of octreotide [13]. This may also explain why a survival gain is significant only in patients surviving for more than 6 months, proving that SSAs are by no means rescue drugs.

An additional explanation is the variability of SSTRs’ expression profile among tumors, as many of the aforementioned studies clearly show that the treatment response rates often depend on SSTRs’ expression.

A critical factor for tumor response may be the serum concentration of SSAs. This is possible as octreotide reduction in cellular proliferation was observed only at a concentration of $10^{-8}$ mol/L. Therefore, monitoring drug serum levels may be mandatory, at least in clinical studies [14].

The negative results of some studies might be explained by these observations, but they still fail to explain the discrepancies between the conclusions reached by Eastern countries (and Greece) and the West. A possible reason for the discrepancies may be patient selection, since a large number of alcoholic cirrhotics participated in Western trials (up to 60%), reflecting the etiological stratification of their cirrhotic population, while studies from the East have mostly recruited patients with viral cirrhosis. China has mostly HBV-related HCC in contrast to Europe’s proportionally larger ethanol-related HCC [73]. Moreover, in many countries including Japan and North America, HCV-related HCC is very common, as well as steatosis. This was certainly the case in the initial Greek trials which were also reflecting the etiological background of cirrhosis at that time, a situation that has since changed [74]. We pointed out that the few alcoholics in our study had a poor response to SSAs, especially those that continued drinking. This very crucial observation, however, has not been commented upon by researchers in any of the negative trials [43].

There may be an additional explanation for the poor response of alcoholics. A German study found very low levels of weak expression of SSTRs in tissue from alcohol-related HCC patients (only two of their patients had viral HCC) [75].

However, it was the recent observation in a meta-analysis of three phase III immunotherapy trials that provided further support to our ignored suggestions that SSAs may in fact be more effective in viral HCC and not so effective when steatosis is present (as in alcoholic cirrhosis). Indeed, in this study, immune therapy did not improve survival in NASH-driven HCC patients compared to other etiologies [76].
Kinase inhibitors are probably equally effective in NAFLD-HCC compared to viral HCC. Although current treatment guidelines for HCC do not address etiology as a factor for concern, the time has come for modifications of treatment according to HCC etiology.

Table 2. Summary of the negative studies about the role of somatostatin analogues in the treatment of advanced HCC [77].

| Authors                  | Type of Study               | No. of Patients | SST Receptors Assessment | Intervention                                      | Control                  | Outcomes                                                                 |
|--------------------------|----------------------------|-----------------|--------------------------|--------------------------------------------------|--------------------------|--------------------------------------------------------------------------|
| Rabe C et al., 2002 [61] | Retrospective multicenter cohort study | 63 patients with unresectable HCC and cirrhosis Child A–C | N/A          | Initially: 43 cases received long-acting octreotide 20–30 mg/mo. 20 cases received octreotide 50 t.i.d-300 μg t.i.d. s.c. Later: 11 patients of the s.c. group were converted to long-acting octreotide | None                     | At 3 mos.: • 2 patients showed partial remission • 22 tumors showed no change • 26 tumors showed progression At 6 mos: • 11 tumors showed no change • 15 tumors progressed Median survival was 9 mos. |
| Yuen MF et al., 2002 [62] | RCT                         | 70 patients with advanced HCC | N/A          | 35 patients received a 2-week course of 250 μg short-acting octreotide twice daily followed by Sandostatin LAR 30 mg injection once every 4 wks. for 6 doses | 35 patients received placebo | • Long-acting octreotide showed no survival benefit • No difference in the cumulative survival between the 2 groups • No tumor regression and no reduction of serum AFP levels in patients receiving Sandostatin LAR |
| Slijkhuys WA et al., 2005 [65] | Prospective cohort study | 30 patients with advanced HCC | N/A          | Long-acting octreotide 30 mg i.m. every 4 to 6 wks. | None                  | • Median TTP was 3.6 mos. • Median survival was 5.1 mos. • Overall, limited beneficial response in terms of TTP and survival |
| Cebon J et al., 2006 [67] | Observational study         | 63 patients with Scintigraphy | Long-acting octreotide | None                                             |                         | • No major changes in QoL                                                |
| Study                                                                 | Design | Patients | Treatment | Response                                                                 |
|----------------------------------------------------------------------|--------|----------|-----------|--------------------------------------------------------------------------|
| Sanoff HK et al., 2015 [68] Multicenter observational study          | RCT    | 24 patients with advanced HCC (46% metastatic disease) | Pasireotide LAR 60 mg i.m. monthly + everolimus 7.5 mg per os daily | 2% of the patients had partial tumor response  
6% of the patients showed a decrease a more than 50% decrease of serum AFP levels  
Median survival was 8 mos.  
Median TTP was 3.5 mos.  
Median survival was 6.7 mos.  
10 patients had stable disease as the best response. |
| Verset G et al., 2007 [69]                                           | RCT    | 109 patients with advanced HCC                           | 56 patients were treated with octreotide LAR + TAM  
53 patients were treated with TAM | No difference between the groups concerning:  
Tumor regression  
AFP decrease  
Improvement of QoL survival |
| Becker G et al., 2007 [70]                                           | RCT    | 120 patients with advanced HCC                           | 60 patients were treated with long-acting octreotide 30mg i.m. monthly  
59 patients were treated with placebo | No difference in cumulative survival  
The median time until definitive global health score deterioration was 2.3 mos. in the octreotide and 4 mos. in the placebo group  
Median OS was 6.53 mos. for octreotide versus 7.03 mos. for placebo  
PFS did not differ significantly between the two treatment groups  
No objective responses were achieved in the octreotide group but 33% of patients achieved disease stabilization for a mean time of 5.5 mos. |
| Barbare JC et al., 2009 [71]                                         | RCT    | 272 patients with untreatable or relapsed HCC             | 135 patients were treated with long-acting octreotide 30 mg i.m. monthly for 2 years  
137 patients were treated with placebo |  
| Abbrev.: RCT, randomized controlled trial; HCC, hepatocellular carcinoma; s.c., subcutaneous; i.m., intramuscular; b.i.d., twice a day; mo(s), month(s); N/A, not applicable; OS, overall survival; AFP, a-fetoprotein; wk(s), week(s); TAM, tamoxifen; t.i.d., three times a day; TTP, time to tumor progression; PFS, progression free survival; QoL, quality of life. |
4. Is There a Place for SSAs in the Treatment of HCC Today?

A comparison of the survival results between SSAs and kinase inhibitors or the recently introduced checkpoint inhibitors could provide an answer to this question. As secondary parameters, side effects and cost of treatment should also be examined. However, it should be kept in mind that only indirect conclusions can be drawn, as there are no direct, head-to-head comparisons available.

Parameters of progression such as time to progression and progression-free survival may not represent treatment failure, as they are not in fact a surrogate marker of survival. The real endpoints in clinical trials should be overall survival [78] and to a lesser extent, quality of life.

HCC tumors are characterized by high vascularization and several local abnormalities of the immune reactions. Increased Treg expression is associated with poor prognosis and metastatic disease [79], as well as overexpression of the checkpoint inhibitors programmed cell death protein 1 (PD-1) and programmed cell death protein ligand-1 (PD-L1) [80]. Clinically, PD-L1 expression is associated with increased tumor recurrence risk and poor prognosis [81]. Therefore, it is only logical that anti-angiogenic kinase inhibitors and immune checkpoint inhibitors (ICI) are the two treatment modalities that have shown efficacy in HCC. Combination of anti-angiogenics and ICI seems to be synergistic, because vascular endothelial growth factor (VEGF) inhibition improves the survival of cytotoxic T lymphocytes and decreases Tregs infiltration, thus providing a favorable immune microenvironment for the ICI anti-tumoral effect [82,83]. An elegant review on the mechanisms of action of immune checkpoint inhibitors has recently been published [82].

In 2007, the FDA approved sorafenib for the treatment of advanced HCC, despite the rather limited survival gain from 7.9 to 10.7 months [84]. The response rates were consistently low, probably due to the tumor heterogeneity. In one trial, the median survival gain was again only 2–3 months in Asian and Caucasian patients [85]. It is pertinent in our comparisons that large non-interventional observational studies have shown that the survival of patients with Child B cirrhosis on sorafenib is significantly shorter when compared to Child A patients. No conclusive evidence for a benefit in Child B patients was provided. Therefore, it is suggested that the use of sorafenib should be limited to patients with well compensated stages of cirrhosis [86].

Lenvatinib is a multi-kinase inhibitor approved in 2018 with a better survival benefit for HBV-related HCC than sorafenib. Since then, three second-line drugs, Regorafenib, Cabozantinib and Ramucirumab (a VEGF-2 receptor inhibitor), were approved for patients not responding to sorafenib. However, none improved the overall survival, the progression-free survival or life quality significantly [87]. Specifically, the overall survival was reported to be 13.6 months for Lenvatinib, 10.6 months for Regorafenib, 10.2 months for Cabozantinib and only 8.5 months for Ramucirumab [3,83,88]. These survival data are very similar (if not lower) than those reported in many SSA trials, with the exception of those selecting moribund cirrhotics or trials selecting a substantial number of patients with alcoholic cirrhosis or are also active drinkers.

The relative success of immunotherapy in several neoplasms prompted its application in HCC.

Two recombinant monoclonal human immunoglobulin IgG4 antibodies specific for human PD-1, nivolumab and pembrolizumab, received accelerated FDA approval as second-line therapies for advanced HCC based on very recently updated data from phase II studies [89]. However, in a phase III trial the median overall survival was 13.9 months in the pembrolizumab arm compared to 10.6 months of the placebo arm [90], and a similar overall survival of 16.4 months versus 14.7 months with sorafenib was reported for nivolumab [91]. These results are again comparable to SSA trials. Given the not convincing data of phase III trials, the European Medicines Agency (EMA) has not approved either agent for treatment of patients with HCC [92].

Currently, the holy grail of ICI is the search for effective combinations of a kinase or VEGF inhibitor with an ICI [93]. The only combination that has reached a phase III trial is
that of atezolizumab plus bevacizumab with patients on sorafenib being the control arm [94].

In the first randomized study, mostly patients with Barcelona stage C were included (15% stage B, 2% stage A), all of them Child A with 5 and 6 points. It is important to note that 70% of recruits in both arms were viral-related cirrhotics. The latest report on overall survival presents 22 months of survival for the combination and 13.4 months for the sorafenib group [95]. A total of 336 patients received atezolizumab plus bevacizumab and 165 received sorafenib with a median follow up of 15.6 months. The median OS was 19.2 months with the combination and 13.4 months with sorafenib (p < 0.001). However, the complete response was very low for both regimens. Better survival, as expected, was observed in Barcelona B than C (both regimens) and much better in viral-related HCC than in non-viral HCC. Based on these results, the combination is currently the recommended first-line treatment of advanced HCC. However, the increased efficacy was obtained at the cost of a high incidence of grade 3–5 toxicity.

Moreover, a smaller real-world trial reported a median overall survival of 15.0 months for Child A patients and only 6.0 months for Child B patients [96].

Extensive overviews of immune checkpoint inhibitors were very recently published [97–100], describing mechanisms of drug resistance as well [101,102].

A second combination trial of Lenvatinib and pembrolizumab (KEYNOTE-524) also reported an overall survival of 22 months, but these were findings of a phase Ib study. Results of a phase III trial are pending [103]. Admittedly, the reported survival of 22 months is the best one yet, but it remains to be confirmed in real-world studies. Moreover, a combination trial with an SSA as one of the two components would be a very interesting proposition in view not only of survival results and the anti-angiogenic effects of SSAs, but also of serious side effects reported in the combination trials. Synergistic immunomodulation is often accompanied by synergistic toxicity, as exemplified in KEYNOTE-524, in which the combination of Lenvatinib with pembrolizumab shows an overall response rate of 36% but also a 67% incidence of treatment-related side effects of grade 3 or worse [103]. By contrast, SSAs’ side effects are limited to moderate diarrhea and some degree of hyperglycemia easily controlled.

New trials of immunotherapy are currently underway [104].

The cost of the new treatments, either monotherapies or combinations, is considerably higher than SSA treatment and certainly pose a serious burden in weak economies particularly in the era of the SARS-CoV-2 pandemic. Thus, treatment with atezolizumab plus bevacizumab offered only 0.530 quality-adjusted life years (QALYs) and an incremental cost of USD 89,807 over sorafenib, which had an incremental cost-utility ratio of USD 169,223 per QALY gained. Atezolizumab plus bevacizumab treatment is therefore not a cost-effective alternative when compared with sorafenib [105].

Finally, even in the different setting of recurrence prevention after a curative hepatectomy, the administration of a different approach immunotherapy based on CIK (cytokine-induced killer cells) has produced conflicting results. A phase III study reported a median time of recurrence-free survival of 44.0 months in the immunotherapy group compared to 30.0 months of the control group [106], but another phase III trial reported different results, with a recurrence-free survival of 13.6 months for the treatment group and 7.8 months for the controls [107]. Since no data for a similar use of SSAs exist, no comparisons can be made.

There is an important point that all reported trials of new drugs have in common: they all included B or C BCLC stage (with occasional A stage) patients who were also almost 99% Child Pugh A classification, in contrast to most SSA-negative trials that rarely included Child Pugh A patients. Moreover, numerous exclusion criteria and adverse effects were applied which were not applied in SSAs treatment trials. Thus, Child Pugh B and C patients are consistently excluded, even those with moderate ascites and HIV co-infection (4). BCLC new stratification recommends systemic treatment only at stages B and C and not D (moribund with expected survival of only 3 months), as in most octreotide-negative trials [64].
5. Future Research

Many molecular mechanisms have been clarified in the pathogenesis of HCC, including HBV gene integration, genomic instability caused by mutation and activation of cancer-promoting signaling pathways. New mechanisms, such as epigenetics, exosomes, autophagy, metabolic regulation and immune suppression, are continually under intense investigation [108]. A recent study using a decision tree analysis described eight HCC phenotypes with variable cancer risks [109]. Four immunovascular subtypes were recently described [110].

Trials based on newer molecular and genetic classifications of HCC may lead to better selection of patients suitable for SSA treatment. Results on HCC related to non-alcoholic liver disease should also be investigated. Since octreotide (and possibly other SSAs as well) inhibits cell proliferation in certain concentrations, it is advisable that serum levels are frequently monitored in future trials.

Most importantly, direct comparisons with kinase inhibitors or immune checkpoint inhibitors should be performed, since indirect comparison suggested a potentially relevant antineoplastic activity, at a low cost and with very few side effects.

Combination treatment modalities should also be performed. Moreover, a clinical trial investigating a possible role of SSAs as adjunct therapy after radiofrequency ablation (RFA), transarterial chemoembolization (TACE) or surgery in patients with high risk of tumor relapse could be very interesting, as small, mostly uncontrolled trials have been very promising in these settings.

6. Conclusions and Recommendations

Somatostatin analogues are by no means magic bullets. It is totally inappropriate to give treatment to moribund patients, as many negative studies have performed. Conflicting results could also depend on the heterogeneous population enrolled in different studies. Indeed, positive studies had a high proportion of HBV- and HCV-related HCC and a low proportion of alcohol-related HCC. Patients with alcoholic-cirrhosis-related HCC do not respond equally well. This may explain the better results in patients from Greece and the East. China has mostly HBV-related HCC compared to the higher percentage of ethanol-related HCC in Europe. Moreover, in many countries including Japan and North America, HCV HCC is common [73] and it is usually associated with steatosis that may affect results.

In all probability, SSAs are not inferior to multiple-kinase or VEGF inhibitors and not inferior to the monotherapy with ICIs. Therefore, direct comparison trials are justified. The combination therapy seems to be superior to SSAs, but combinations with SSAs may be equally effective at a fraction of the cost and with much less toxicity.

In future trials of HCC systemic therapy, patient selection is mandatory. Patient cohorts should be carefully matched for underlying etiology and disease stage. Current evidence indicates that SSAs are suitable for patients with virally induced cirrhosis, ideally after identification of the presence of SSTR2 and SSTR5 with scintigraphy or, even better, on tumor tissue after a liver biopsy. Candidates are those classified as BCLC stage B or C, Child Pugh A, which is the same indication for TACE and kinase inhibitors or ICI therapy. If a long-acting somatostatin analogue is used, it would be reasonable to add a short-acting analogue during the first two months in order to ensure high enough plasma levels from the initiation of the treatment [111]. Quality of life is an important end point in this kind of trial, but direct trials have to be conducted to compare SSAs with kinase inhibitors or ICIs in that respect. Classification of HCC is becoming more accurate, and new molecular classification based on single-cell analysis is under way [112]. Homogeneity of clinical trials will therefore be improved, and better selection of patients is to be expected with the new and promising very simple CRAFITY classification [113,114]. It is hoped that new classifications based on HCC different molecular abnormalities will further improve the
validity of trials. In the end, however, every trial should be focused on the hard final point, which is survival [78].

In conclusion, we believe that SSAs may have a place even today, although more detailed studies based on careful patient selection are definitely required. After careful selection of patients according to the recent BCLC strategy [64], approximately 40% of HCC patients respond to the administration of SSAs with a significant survival gain and improvement in their quality of life, but this is mostly based on observational studies. Some groups of patients, such as the Octreoscan-positive or those with viral-related HCC, are better candidates for this treatment.

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