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Selective Internal Radiation Therapy (SIRT) Versus Sorafenib in Mongolian Patients with Advanced Hepatocellular Carcinoma: A Subgroup Analysis of the SIRveNIB Study.

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Objective: The purpose of this study was to compare the efficacy and safety of selective internal radiation therapy and sorafenib on advanced hepatocellular carcinoma. **Methods:** The National Cancer Center of Mongolia was one of the Asia-Pacific Liver Cancer Research Team sites, and we recruited patients into the study. Patients were randomly assigned 1:1 stratified and to receive either SIRT or sorafenib 800 mg/d orally. Outcome measures were physical examination, functional assessment, CBC, liver function test, AFP results, and CT scan every 4, 8 and, 12 weeks after treatment initiation. **Results:** Between March 2011 and June 2016, 39 patients were enrolled in the study. Twenty patients were treated with SIRT, and 19 patients were treated with sorafenib. Median OS and PFS rates were no different in sorafenib arm patients than in SIRT arm (15.56 vs. 9.17; HR 0.95, 95% CI 0.46, p = .889) and (8.51 months vs. 5.85 months; HR,1.07; CI, 0.53-2.16, p = .842). But, tumor response was greater in SIRT than sorafenib treatment (68.8% vs 62.5%, p = .033). Two (10%) patients had a complete response, 2 (10%) patients had a partial response, and 7 (43.8%) patients had a stable response. A total of 165 treatment-emergent adverse events were reported (SIRT 66 vs. sorafenib 99). Significantly fewer patients in the SIRT than sorafenib group had grade ≥3 adverse events (83 vs. 115, p = .0964). **Conclusion:** In patients with locally advanced hepatocellular carcinoma, overall survival did not differ significantly between SIRT and sorafenib. But SIRT significantly increased tumor response and reduced the incidence of adverse events compared with sorafenib.

Keywords: RECIST, SIRT Selective Internal Radiation Therapy, Alanine Aminotransferase, Aspartate Aminotransferase

Introduction

Liver cancer is a common disease in the world's population, the fifth most common cancer with the second-highest cancer mortality worldwide[1,2]. One million new cases of primary liver cancer are detected each year, which indicates an increasing trend[3]. In Mongolia, primary liver cancer is the most common cancer, and 2000-2300 new cases have diagnosed each year[4]. Of patients diagnosed, 79.5% are in the advanced stages, having stage III and IV disease. These patients have few effective treatment options and poor prognosis[5].

Most cases of liver cancer (70-80%) are found in Asian countries. Consequently, public health issues of the region, prevention from infection, health education, and quality of life have become of particular importance[6]. Approximately 25% of patients diagnosed with liver cancer can be treated, and resection surgery, radiation therapy, and drug treatment are mainly performed[7].

Selective Internal Radiation Therapy (SIRT) with yttrium-90 resin microspheres is one potential alternative treatment for locally advanced hepatocellular carcinoma[8]. SIRT enables targeted delivery of radiation to the tumors, while largely sparing the surrounding liver parenchyma. A meta-analysis showed a high response rate to Y-90 SIRT in hepatocellular carcinoma patients. Population disparity prevented the assessment of overall survival in this meta-analysis, but cohort studies of patients with hepatocellular carcinoma receiving SIRT report median overall survival between 7.0 and 26.3 months[7-9].

Sorafenib is an oral multikinase inhibitor with antiproliferative and antiangiogenetic effects. It has been shown to inhibit the activity of the serine/threonine kinases c-Raf (Raf-1) and B-Raf; the mutagen-activated protein kinases MEK and ERK; vascular endothelial growth factor receptors (VEGFR)-1,2 and 3[10-13]. In the multicenter, double-blind, randomized phase III Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) study, sorafenib was shown to be efficacious and well-tolerated in patients with advanced hepatocellular carcinoma. The median overall survival was 10.7 months (95% CI, 9.4-13.3)[14].

We are not aware of a randomized phase III trial comparing SIRT and sorafenib in the Asia-Pacific region. The Asia-Pacific Liver Cancer Research Team initiated a study comparing the efficacy and safety of SIRT versus sorafenib dosing in patients with locally advanced hepatocellular carcinoma and conducted at centers in the Asia-Pacific region. As part of this study, we conducted the "Phase III multi-center clinical trial on the treatment of advanced hepatocellular carcinoma by selective internal radiation therapy (SIRT) and sorafenib" with a team of Asia-Pacific centers.

Our research focused on analyzing the effectiveness and safety of sorafenib and selective internal radiation therapy, which are the most successful treatments currently available in advanced hepatocellular carcinoma.

Materials and Methods

Participants and outcome measures

The study enrolled patients in 11 countries in Asia with locally advanced hepatocellular carcinoma between March 2011 to June 2016, and AHCC06 reached a milestone with the recruitment of 360 patients on May 22, 2016. The National Cancer Center of Mongolia enrolled 39 patients in the study from March 2011 to June 2016. Patients were randomly assigned 1:1 to receive either SIRT or sorafenib 800 mg/d orally.

Outcome measures were physical examinations, level of function, CBC, liver function tests, and AFP results every four weeks or at 4, 8, and 12 weeks follow up visits after treatment initiation. Tumor response was assessed by a contrast CT scan every 12 weeks from the date of randomization. Median overall survival, time to tumor progression, progression-free survival were estimated using Kaplan-Meier plots with corresponding two-sided 95% CIs. The two groups were compared using the Cox regression analysis based on the hazard ratio. Tumor response was assessed according to RECIST criteria[15].

Patients

All patients were ≥18 years of age, had measurable disease (defined as ≥1 lesion of ≥10 mm), adequate renal function (creatinine ≤2.0 mg/dL), hemopoietic function (leucocytes ≥2.500/μL; platelets≥80.000/μL; hemoglobin >9.5 g/dL) and Eastern Cooperative Oncology Group (ECOG) Performance Status[15] 0 or 1. In addition, eligible patients were required to have: 1) sufficient liver function for safe radioembolization, defined as: an absence of ascites or synthetic liver dysfunction (total bilirubin < 2.0 mg/dL, International Normalized Ratio (INR) ≤ 2.0; albumin ≥ 2.5 g/dL, and aspartate transaminase (AST), alanine transaminase (ALT) and alkaline phosphatase (ALP)

each ≤ 5 × upper limit of normal, 2) hepatic arterial anatomy that enabled safe delivery of microspheres to the liver only, 3) without excessive hepato-pulmonary shunting (20%), and 4) absence of main trunk portal vein thrombosis. Premenopausal, sexually-active individuals were required to use two forms of contraception during the study. Patients were excluded if they were pregnant or breastfeeding or had been previously treated with external beam radiotherapy to the liver or were currently receiving any other investigational agent.

SIRT treatment arm

Patients randomized to SIRT received SIR-Spheres® Y-90 resin microspheres (Sirtex Medical Ltd., Australia) as the patient-specific prescribed medication within 35 days after signing the informed consent form, and after the baseline assessment of their suitability for the procedure. The evaluation comprised a hepatic angiogram, and liver-to-lung shunt pre-assessment with Technetium-99 m (^{99}mTc)-labelled human serum albumin. The hepatic angiogram determined the vascular anatomy of the liver to plan the optimal delivery of the SIR-Spheres. The 99Tc lung-shunt study assessed the presence and degree of lung shunting from the liver. Patients randomized to SIRT, but who are found to be unsuitable for treatment were included in the SIRT intention to treat analysis. The prescribed activity of SIR-Spheres calculated based on the patient's body surface area model or the partition model. If the body surface area method was used for dose calculation and the percentage lung shunting exceeded 20% of the hepatic artery blood flow, as determined by ^{99m}Tc-scan, the partition model was used to adjust the prescribed dose so that the radiation absorbed dose to the lungs did not exceed 20Gy.

Sorafenib treatment arm

Oral treatment with sorafenib (Nexavar, Bayer HealthCare Pharmaceuticals, Inc., Germany) commenced 400 mg twice-daily the week following randomization. Treatment in the sorafenib arm was commenced within one week after randomization. Patients received oral sorafenib, 400 mg twice daily. Sorafenib treatment continued until there was evidence of treatment failure (lack of efficacy resulting in tumor progression at any site determined by CT or MRI scan); there was cure or complete response and/or the patient underwent surgical resection, liver transplantation or ablative therapy, unacceptable toxicity occurs, or the patient requested an end to treatment. As published previously, doses may be delayed and/or reduced for clinically significant haematological toxicities and other toxicities or adverse events related to study therapy[16]. Dose reductions first to 400 mg/day and then to 400 mg every second day were allowed, and if further dose reductions were required, the medication was discontinued. For non-hematological adverse events other than skin toxicity, the treatment was interrupted for any grade 3 adverse event, and the dose subsequently reduced by one level. For skin toxicity, the treatment interrupted for any grade 2 or grade 3 event, and a decreased dose frequency or level was subsequently considered. The dose was re-escalated once the toxicities or adverse events had resolved[17].

Assessment and follow-up

A quadriphasic contrast-enhanced spiral CT scan of the abdomen/pelvis was performed to diagnose hepatocellular carcinoma, according to the American Association for the Study of Liver Diseases criteria, and to determine the extent of liver disease and to exclude extrahepatic abdominal or pelvic metastases. A biopsy positive for hepatocellular carcinoma was required for diagnoses if the tumor did not fulfill the radiological criteria. A thoracic CT scan was used performed to exclude lung metastases. MRI scans were used instead of CT scans in patients for whom CT scanning is not clinically feasible. Each of these CT series was performed less than 28 days before informed consent was received. All radiology images in this trial were centrally reviewed by treatment-blinded radiologists at the National Cancer Center Singapore.

Assessments were at 4-week intervals for the first three months, and then 12-week intervals thereafter. Following treatment, patients were followed for survival or death at 12-week intervals.

Each patient's status was categorized as disease progression, death, complete regression, unacceptable toxicity, the patient undergoing surgical resection, liver transplantation, or ablative therapy due to a sufficient response to the treatment, loss to follow-up, or a request to withdraw.

Statistical analysis

Median overall survival, time to progression, and progression-free survival were estimated using Kaplan-Meier plots with corresponding two-sided 95% CIs. Demographic characteristics with categorical variables (gender, and hepatitis status) were

compared between SIRT and sorafenib groups using Fisher's exact test. Ages of the patients in the two treatment groups were compared using the two-sample independent t-test. Toxicity was assessed using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 created by the U.S. Department of Health and Human Services. Adverse events were reported from the date of consent to patient death. If an adverse event increased in severity over the next defined interval, it was recorded as a new event in the next interval. Cox regression was used to investigate adverse events.

Outcomes measures

Definitions

- Overall survival - the time from the date of randomization to death from any cause.
- Time to progression - the time from the date of randomization to tumor progression at any site in the body.
- Progression-free survival – the time from the date of randomization to tumor progression in the liver or death or death whichever is earlier.
- Tumor response rate - the number of patients whose best overall response rate (best tumor response over the whole study between randomization and the last tumor assessment) is the partial response or complete response, divided by the total number of patients in the analysis population.
- Disease control rate - the number of patients whose best overall response is partial response, complete or stable disease, divided by the total number of patients in the analysis population.
- Health-related quality of life - assessed using the EQ-5D questionnaire[18].
- Adverse events - reported according to (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] Version 4.02)[19].
- Functional status – reported using the Eastern Oncology Group Performance Status, which is a simple measure of functional status ranging from 0 to 5.

All analyses were performed using the intention-to-treat principle, where patients were analyzed according to their randomized group. The determination of the primary outcome (overall survival) was an unadjusted log-rank test used to test, and a proportional hazards model used to estimate the hazard ratio together with the corresponding 95% confidence intervals (CI). Time to event curves (for overall survival and progression-free survival) were displayed using the method of Kaplan-Meier.

The tumor response rate, disease control rate, and the rate of down-staging to surgical resection, radiofrequency ablation, or liver transplantation compared between treatments using appropriate tests for proportions.

Ethical statements

The Ethics Committee of Minister of Health Science Mongolia approved this study protocol on February 24, 2011 (Ethical approval number 10). The study protocol was approved by the Ethics Committee of Minister of Health Science Mongolia on February 24, 2011. The National Cancer Center of Mongolia complied with the provisions of the Good Clinical Practice guidelines and the Declaration of Helsinki and local laws.

All patients provided written informed consent before enrollment in the study. An Independent Data Safety and Monitoring Board monitored safety and efficacy.

Results

Between March 2011 and June 2016, 39 Mongolian patients were enrolled in the study. Those were divided into two groups by a randomized sampling method. Nineteen patients were treated with sorafenib, and 20 patients were treated with selective internal radiation therapy (Figure 1).

The average age was 56.7 ± 8.35 years, 59% patients were diagnosed at Eastern Oncology Group Performance Status 1, 41% diagnosed with hepatitis B and 30.8% had hepatitis C. Of 17.9% patients with portal vein thrombosis, 61.5% diagnosed with Barcelona Clinic Liver Cancer Stage C, 92.3% were at Okuda stage I, 84.6% at Child-Pugh stage A and 71.8% patients were at stage III of the Child-Pugh classification (Table 1).

Patients in the sorafenib group experienced the following common adverse events: hypertension, ascites, palmar-plantar erythrodysesthesia syndrome, rash, diarrhea, and constipation. Also, ALT, AST, bilirubin results in liver function tests were 3-4 times higher in the sorafenib group. For the AFP results, 3 (7.6%) patients out of 17 in the sorafenib group decreased 50% from the date of random assessment versus 6 (40%) patients out of 15 in the SIRT group ($p = .12$).

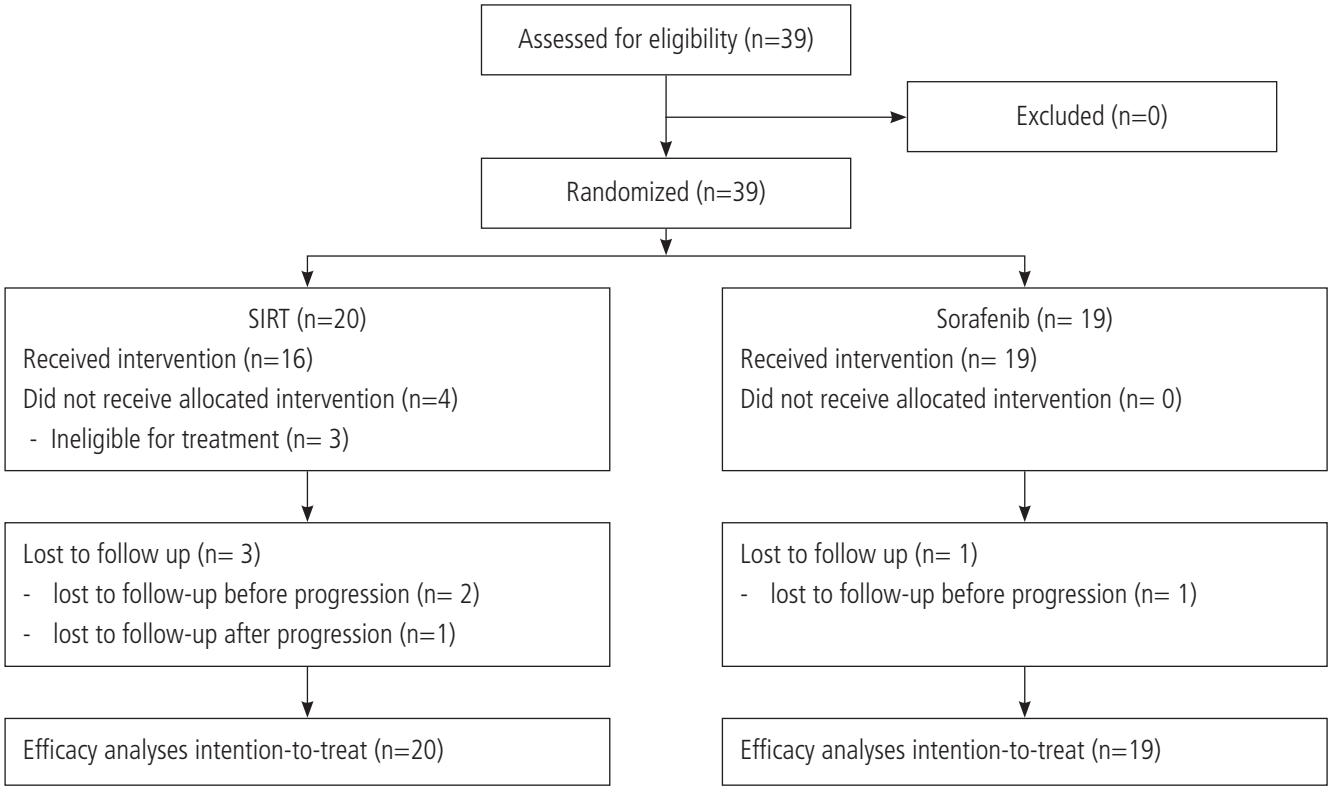

Figure 1. Subject disposition

Table 1. Baseline patient Characteristics

Characteristics, n (%)	SIRT (N = 20)	Sorafenib (N = 19)
Portal vein thrombosis		
Yes	3 (15.0%)	4 (21.1%)
No	17 (85.0%)	15 (78.9%)
ECOG*		
0	9 (40.0%)	7 (36.8%)
1	11 (60.0%)	12 (63.2%)
Child-Pugh stage		
A	17 (85.0%)	16 (84.2%)
B	3 (25.0%)	3 (15.8%)
Barcelona Clinic Liver Cancer stage		
B	7 (35.0%)	8 (42.1%)
C	13 (65.0%)	11 (57.9%)
OKUDA stage		
I	17 (85.0%)	16 (84.2%)
II	3 (15.0%)	3 (15.7%)
TNM stage		
II	1 (5.0%)	2 (10.5%)
IIIA	14 (70.0%)	13 (68.4%)
IIIB	5 (25.0%)	4 (21.1%)

*Eastern Oncology Group Performance Status Score

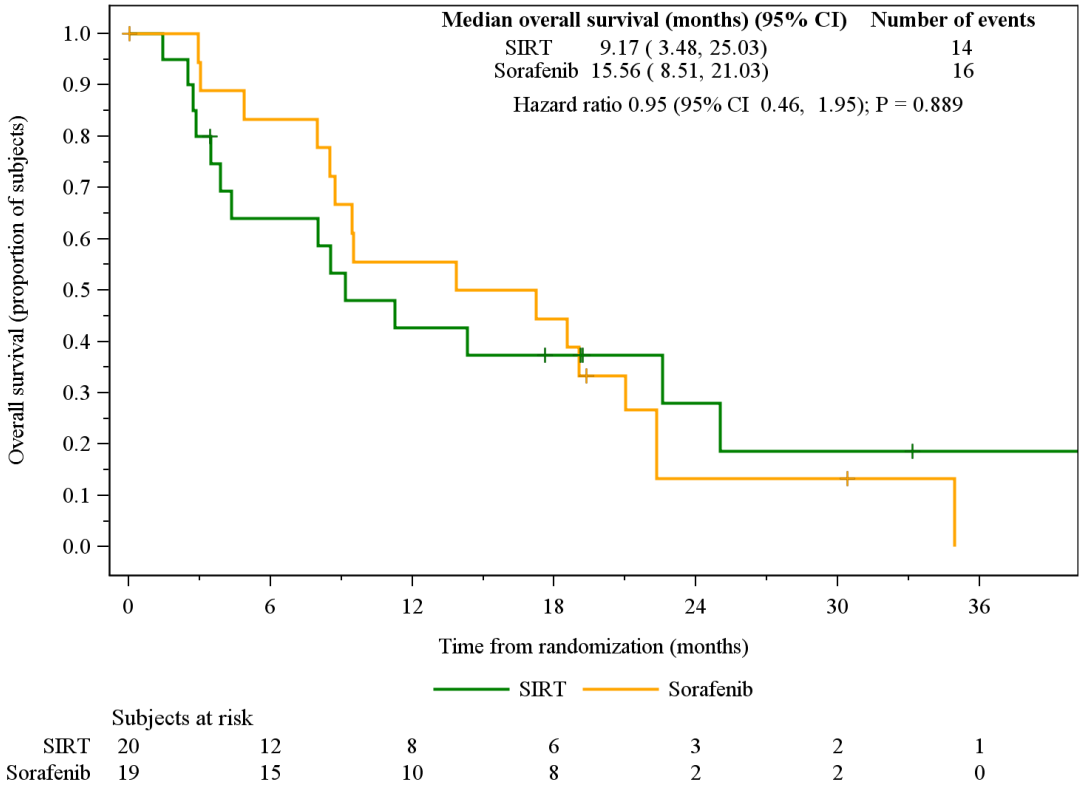

Figure 2. Kaplan-Meier plot for the overall survival of the 39 Mongolian patients.

Overall survival

We did a follow-up assessment of the 39 Mongolian patients up between March 2011 and February 2017 and evaluated the overall survival of all patients. There was no statistically significant survival difference in sorafenib arm patients than in SIRT arm (15.56 vs. 9.17 months; HR 0.95, 95% CI 0.46; p = .889) (Figure 2).

Response rate and disease control rate

The tumor response results were greater in SIRT than sorafenib. Of 2 (10%) patients got full response, 2 (10%) patients got partial response and 9 (45%) patients received stable responses. In overall response in SIRT arm was better than sorafenib ar. (20 vs. 0%, p = .001) (Table 2).

Progression-free survival and time to radiologic progression

The progression-free survival time was not statistically significantly different in sorafenib arm patients compared to the SIRT arm (8.51 vs. 5.85 months, HR 1.07, CI, 0.53 - 2.16, p = .842). In total, 165 treatment emerged adverse events were reported over the study period, 66 in the SIRT group, and 99 in the sorafenib group.

Safety and health-related quality of life

In total, 165 treatment-emergent adverse events were reported over the course of the study; 66 in the SIRT group and 99 in the sorafenib group. Fewer patients in the SIRT group than in the sorafenib group experienced one or more adverse events:

Dermatological events (specifically, palmar-plantar erythrodysaesthesia syndrome and rash) and diarrhea occurred at a higher frequency in the sorafenib group than in the SIRT group (Table 3).

Also, the liver function test results (ALT, AST, and bilirubin) were 3-4 times higher in the sorafenib group. The AFP decreased 50 percent in 3 (7.6%) of 17 patients in the sorafenib group from the date of randomization compared to 6 (40%) of 15 in the SIRT group.

Discussion

In our study, we found SIRT failed to demonstrate superiority or detriment compared to sorafenib in the treatment of locally

Table 2. Response rate and disease control rate.

Characteristics, n (%)	SIRT (n = 20)	Sorafenib (N = 19)	p-value
Complete response (CR)	2 (10.0)	0	
Partial response (PR)	2 (10.0)	0	
Stable disease (SD)	7 (35.0)	10 (52.6)	
Progressive disease at liver	2 (10.0)	3 (15.8)	
Progressive disease at any site	3 (15.0)	3 (15.8)	
Not done/not evaluable	4 (20.0)	4 (20.0)	
Tumor response rate (CR + PR)	4 (20.0)	0	.001
Disease control rate (CR + PR + SD)	13 (55)	10 (52.6)	1

Fisher's exact test

Table 3. Summary of treatment-emergent adverse events by treatment

System organ class preferred term	SIRT (N = 16)	Sorafenib (N = 19)	p-value*
Ascites	1 (6.3)	4 (21)	.6081
Diarrhea	0	7(36.8)	.001
Rectal hemorrhage	0	1 (5.3)	1
Vomiting	0	1 (5.3)	1
Fatigue	0	2 (5.3)	1
Decreased appetite	0	3 (5.3)	1
Hyperglycemia	0	1 (0)	1
Hypoalbuminaemia	0	1 (5.3)	1
Palmar-plantar erythrodysaesthesia syndrome	0	9 (47.3)	.001
Hypertension	0	3 (15.8)	.233

*Fisher's exact test

advanced hepatocellular carcinoma. The tumor response ratio and adverse event frequency were, however, improved with SIRT over sorafenib. Together with the SIRveNIB study, this is the first large-scale prospective study to compare these treatments and provide evidence that SIRT may offer a better-tolerated alternative to sorafenib in the Asia-Pacific region[20].

The overall survival in the sorafenib arm of our study was better than that observed in the sorafenib arm of SIRveNIB (5-month-long study) and he SHARP trial in Europe, North America, South America, and Australia (11 months)[21]. However, the SIRveNIB population differed slightly from that included in these studies; SIRveNIB excluded extrahepatic involvement at baseline as the aim of the study was to compare a systemic treatment with a liver-directed treatment. In our study, 61.5% of the population was Barcelona Clinic Liver Cancer Stage C, whereas this proportion was 4% in the Asia-Pacific trial and 17% in the SHARP trial.

The SARAH study has a similar design to SIRveNIB but was conducted in a European population, where the etiology of hepatocellular carcinoma differs from that in the Asia-Pacific population, where it is primarily due to viral hepatitis. The initial results of SARAH suggest that as in SIRveNIB and our study, there was no statistically significant difference in overall survival between the SIRT and sorafenib groups (8 months and 10 months, respectively, p = .179). SIRT was similarly better tolerated than sorafenib with significantly better health-related quality of life.

In our study, SIRT produced a significantly better tumor response than sorafenib. In the intention-to-treat population, a trend towards a longer time to progression and progression-free survival (at any site and in the liver) was suggested, and this was significant in the treated population. The large proportion of intention-to-treat patients assigned to the SIRT arm but not receiving SIRT (29%) can provide a rationale for the favorable

effects of SIRT on secondary endpoints in the treated population. Treated patients may represent an enriched population with better outcomes when treated with SIRT.

Limitations

The study paper reported the results of 39 patients treated at the National Cancer Center of Mongolia during 2011 - 2016. Unfortunately, our analysis of 39 patients was unable to detect a statistically significant difference in efficacy and safety between treatment groups because there were insufficient data to detect any but the largest differences. So, we are unable to determine which treatment is safer. Also, some patients withdrew voluntarily during the trial, which also made it challenging to draw statistical conclusions. Based on those lessons, we need to focus on recruitment targets, especially patient numbers, and keep the patients until the end of the study in further studies.

Conclusions

In patients with locally advanced hepatocellular carcinoma, overall, the survival did not differ significantly between SIRT and sorafenib. But SIRT significantly increased tumor response and reduced the incidence of adverse events compared with sorafenib.

Conflict of interest

The authors state no conflict of interest.

Acknowledgments

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