Central Asian Journal of Medical Sciences
CAJMS

Original Article

Cent Asian J Med Sci. 2017 Nov;3(3):297-305. https://doi.org/10.24079/CAJMS.2017.11.011

Comparison of Adverse Events Between Selective Internal Radiation Therapy Versus Sorafenib in Locally Advanced Hepatocellular Carcinoma in Mongolia: A Subgroup Analysis of SIRveNIB Study.

Ariunaa Khasbazar[1], Sanduijav Ruvjir[1, 2], Bolormaa Yalhgar[1], Tuyatsetseg Altankhuyag[1], Baatarkhuu Oidov[2]

[1]National Cancer Center of Mongolia, Ulaanbaatar, Mongolia; [2]Department of Oncology, School of Medicine, Mongolian National University of Medical Sciences, Ulaanbaatar, Mongolia

Submitted: July 14, 2017
Revised: September 19, 2017
Accepted: October 10, 2017

Corresponding Author
Ariunaa Khasbazar, MSc
National Cancer Center of Mongolia, Ulaanbaatar 13335, Mongolia
Tel: +976-99081875
E-mail: ariunaa@cancer-center.gov.mn

Objective: This study compared the adverse events associated with selective internal radiation therapy to sorafenib in the treatment of patients with locally advanced hepatocellular carcinoma (HCC). **Methods:** From March 2011 to June 2106, the National Cancer Center of Mongolia recruited 39 patients from Mongolia (19 received sorafenib and 20 received SIRT in Singapore) with advanced hepatocellular carcinoma who had not received surgical therapy into a multicenter study involving a total of 360 patients at 27 sites in 11 Asia-Pacific countries. The study was a phase III randomized-controlled clinical trial comparing sorafenib or SIRT. **Results:** Adverse events for patients receiving sorafenib were predominantly grade 1 or 2 in gastrointestinal, constitutional and dermatologic in nature. The most frequently reported drug-related adverse events in patients treated with sorafenib were hypertension, hand-foot skin reaction, diarrhea, alopecia, fatigue. Common procedure-related adverse events were usually mild (grade 1/2) and included nausea and vomiting (27.7% all grades) and abdominal pain (22.1% all grades), with very few grades 3 or greater adverse events. **Conclusion:** In our analysis of 39 patients, we were unable to detect a statistically significant difference in adverse effects between sorafenib and SIRT treatment groups, likely because there were insufficient number patients in our study.

Key words: Selective Internal Radiation Therapy, Sorafenib, Hepatocellular Carcinoma, Adverse Event, Mongolia

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world, and the third most common cause of death [1, 2]. HCC is estimated to occur at a global rate of more than 1 million new cases annually, with an increasing incidence rate and predominance in developing countries [3].

Approximately 70 – 80 % of HCC are in Asia where it is an important public health concern [4]. Approximately 25% of HCC may benefit from proven ablative therapies that are

potentially curative such as surgical resection or radio-frequency ablation (RFA) [5-7]. Most patients with HCC are diagnosed at intermediate to advanced stages of their disease, for which no generally accepted standard therapy exists [2]. For these patients, treatment options are limited and the prognosis is poor [8, 9]. The only systemic therapy proven to confer survival advantage to these patients is sorafenib [10-12].

Selective Internal Radiation Therapy (SIRT) is a form of radiotherapy that utilizes selective trans-arterial administration of radioactive yttrium90 microspheres [13]. In SIRT, radiation is the main therapeutic mechanism rather than embolization in causing of death of tumor cells [13]. The first comprehensive European experience using SIR-Spheres® for the treatment of patients with inoperable HCC reported an overallbest response rate of stable disease or partial response in 88% of patients byRECIST criteria and median overall survival was 7 months (95% CI, 2 – 12 months) [14].

Sorafenib is an oral multikinase inhibitor with anti-proliferative and anti-angiogenetic 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 [15-18]. In the multicenter, double-blind, randomized phase III Sorafeinb 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) [19].

Mongolia has the highest incidence of liver cancer worldwide with about 1600 cases diagnosed each year. Out of these newly diagnosed liver cancer patients from 2010 to 2015 12% (N=192) underwent surgical treatment, 12% (N=192) received embolization treatment, 8% (N=128) were treated by percutaneous ethanol injection and around 35% (560) were diagnosed at an advanced stage and did not receive treatment at all [20].

We are not aware of a randomized phase III trial comparing SIRT and Sorafienb in the Asia-Pacific region. To our knowledge, no randomized clinical trial has shown a survival advantage over best supportive care in the assessment tolerability of SIRT and Sorafenib treatment in Mongolia. Therefore, the purpose of this study was to identify the adverse events of SIRT and sorafeinb treatment and compare them between in two treatment groups.

Materials and Methods

This study was part of an investigator-initiated multi-center study conducted by the Asia Pacific Hepatocellular Carcinoma Trials Group (AHCC) and enrolled patients in an open label phase III trial. The trial (AHCC06) assessed the impact of SIRT compared to sorafenib on overall survival in the treatment of patients with locally advanced hepatocellular carcinoma (HCC). Patients were recruited from 27 medical centers in 10 Asia-Pacific countries.

The study was registered with the clinical trial registry of the Health Science Authority of Singapore on 13th April 2010, and (http://www.scri.edu.sg/crn/asia-pacific-hepatocellular-carcinoma-ahcc-trials-group/current-trials/). The study enrolled patients between April 2010 to June 2016 and AHCC06 has reached a milestone with the recruitment of 360 patients on 22nd May 2016. The 360 patients were recruited from 27 different medical centers in 10 Asia pacific counties. The centers with the highest recruitment numbers were Yangon GI & Liver Center, Mongolia National Cancer Center and The Medical City, Chulabhorn Hospital and National Cancer Centre of Singapore.

The National Cancer Center (NCC) of Mongolia enrolled 39 patients in the study from March 2011 to June 2016. This

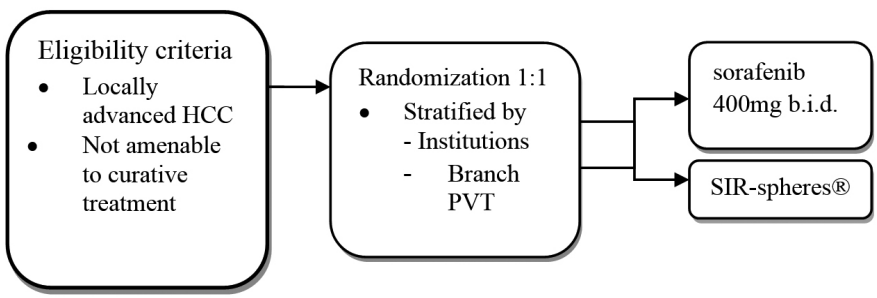

Figure1. Study flow chart

subgroup of patients was the focus of this study. The Ethics Committee of Minister of Health Science Mongolia approved this study protocol in 24th Feb 2011 (Ethical approval number 10). The study protocol was approved by the Ethics Committee of Minister of Health Science Mongolia in 24th Feb 2011. NCC 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.

1. Patients

The protocol for this trial and supporting trend checklist are available as supporting information. Patients with inoperable HCC without distant metastasis and without complete portal vein occlusion were eligible for inclusion. HCC was diagnosed based on radiological criteria for HCC by dynamic contrast-enhanced computed tomography (CT) with supporting evidence based on positive serology for hepatitis B or C virus, or serum alpha-feto protein above normal range (≥400μ/L).

All patients were ≥18 years of age, had measurable disease (defined as ≥1 lesion of ≥10mm), adequate renal function (creatinine ≤2.0mg/dL), hemopoietic function (leucocytes ≥2.500/μL; platelets≥80.000/μL; hemoglobin >9.5g/dL) and Eastern Cooperative Oncology Group (ECOG PS) Performance Status 0 or 1. In addition, eligible patients were required to have:1) sufficient liver function for safe radio-embolization, defined as: an absence of ascites or synthetic liver dysfunction (total bilirubin <2.0mg/dL, International Normalized Ratio (INR) ≤2.0; albumin ≥2.5g/dL and aspartate transaminase (AST), alanine transaminase (ALT) and alkaline phosphatase (ALP) each ≤5×upper limit of normal; 2) hepatic arterial anatomy that would enable safe delivery of microspheres to the liver only; 3) without excessive hepato-pulmonary shunting (20%); and 4) absence of main trunk portal vein thrombosis (PVT). Premenopausal, sexually-active individuals were required to use two forms of contraception during the study. Patients were excluded if they were pregnant or breast feeding or had been previously treated with external beam radiotherapy to the liver or were currently receiving any other investigational agent.

2. Treatment Arm A (Sorafenib)

Oral treatment with sorafenib (Nexavar, Bayer Health Care Pharmaceuticals Inc) commenced 400mg twice-daily the week following randomization. Treatment could be delayed or the dose reduced or discontinued in case of significant toxicities or treatment-related adverse events. Sorafenib treatment was continued until there was evidence of treatment failure (tumor progression at any site), complete response, unacceptable toxicity, the decision to try other HCC therapies, patient's request to stop treatment, or the patient's death.

3. Treatment Arm B (SIRT therapy)

Patients in this multi-center trial received SIRT therapy at designated regional centers in the Asia-Pacific, the main center was the Singapore General Hospital. SIRT is a form of radio therapy during which Y90 microspheres are delivered via a temporary trans-femoral catheter advanced under fluoroscopic guidance by an interventional radiologist into the hepatic artery branches that supply the hepatic lesions. Details of the procedure and post-procedure supportive care associated with Y90-resin microspheres (SIR-Spheres®; Sirtex Medical Limited, North Sydney, Australia) administration have been previously described [21]. Prior to treatment, eligible patients underwent CT or MRI imaging hepatic angiography was conducted to map the hepatic arterial anatomy, determine if coil embolization was required, and determine the extent of hepato-pulmonary shunting using of technetium-99m macro-aggregated albumin (^{99m}Tc-MAA).

Radio-embolization activity (in giga becquerels [GBq]) was calculated using the Partition Model, where feasible, or Body Surface Area (BSA) method when there was multifocal disease for which discrete regions of interest could not be applied or clearly defined. For activity calculations using the partition model, the distribution of ^{99m}Tc-MAA during the simulation were assumed to be identical to Y90-resin microspheres, and the activity was calculated in discrete "areas-of-interest" for the tumor, normal parenchyma and lung compartments, limiting the maximum permitted exposure for the non-tumoral liver compartment to 70Gy and lung exposure to 30Gy. On the day of treatment, ^{90}Y-resin microspheres were selectively infused into the affected lobe (s) or segment (s), or whole liver via a micro-catheter placed in the hepatic artery.

4. Assessment and follow-up

All eligible patients were randomly assigned in 1:1 ratio to receive continuous oral treatment with either 400mg of sorafenib twice a daily under site investigator assessment in

Mongolia and Mongolians who enrolled SIRT therapy group travelled to Singapore to receive SIRT therapy at the Singapore General Hospital. Study randomization was centralized, and assignment to study groups was conducted by computer to achieve a balance between two groups, with stratification before randomization according to institution and absence or presence of partial portal vein thrombosis.

Assessments were made at baseline, and thereafter at 4-week intervals. Baseline imaging assessment was conducted just prior to the start of study therapy and every 12 weeks. Hematological, liver function, and biochemistry tests and physical examination performed every 4 weeks in first 3 months thereafter every 12 weeks.

Adverse events and their severity and relationship to the study treatment were recorded from the date of consent to 28 days after the last dose of sorafenib.

5. Statistical Analysis

Demographic characteristics with categorical variables (gender and hepatitis status) were compared between SIRT and Sorafenib groups using the 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. Adverse events were reported from the date of consent to patient death. If an adverse event increased in severity over the next defined time interval, it was recorded as a new event in the next interval.

Results

From March 2011 to 2016 516 patients were screened in National Cancer Center of Mongolia. Of these patients, 39 met the eligibility criteria and underwent randomization, with 19 patients assigned to the sorafenib group and 20 patients assigned to the SIRT group. These patients were all included in the intention-to-treat analysis. Among the 39 randomized patients, 19 received at least one dose sorafenib and 20 received

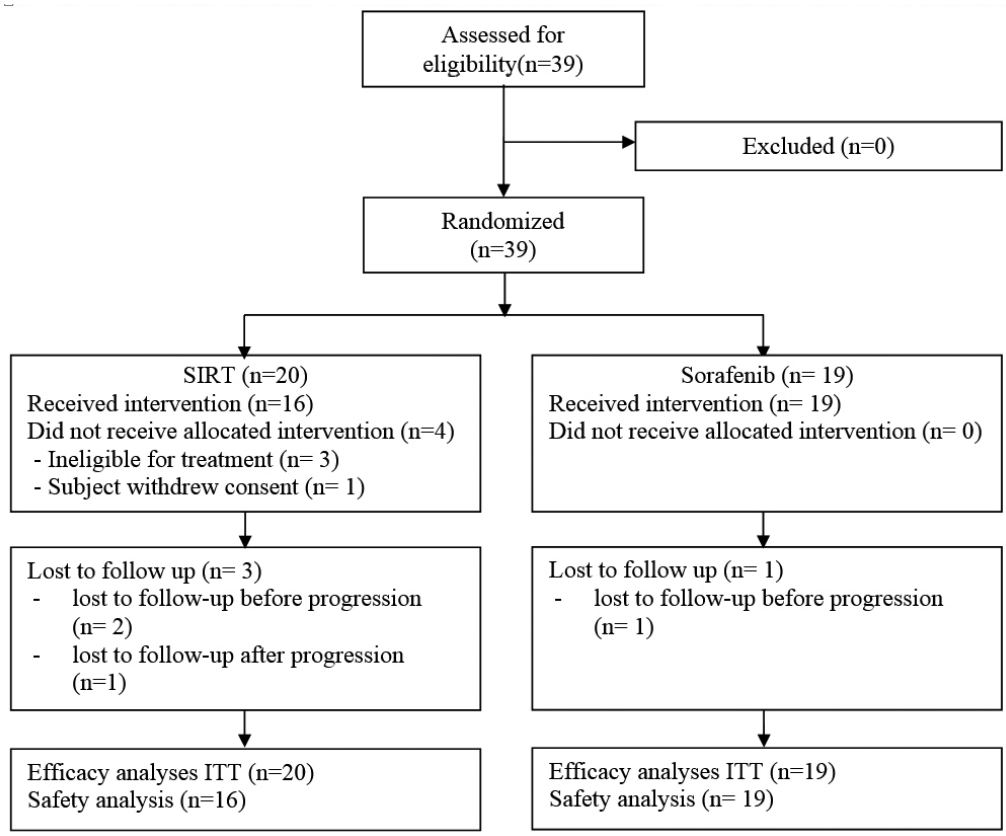

Figure 2. Patient disposition

SIRT treatment; these 39 patients were included in the safety analysis (Figure 1). A total 4 patients were lost follow up. (Figure 2).

The sorafenib and SIRT groups were well balanced with regard to baseline demographic and disease characteristics. Patient characteristics of 39 patients are summarized in Table 1. The median age for the sorafenib group was 57 years (range, 36-71); it was 60 years (range, 39-71) for the SIRT group (Table 1).

The patients in the 2 groups were essentially similar. BCLC C patients without extra-hepatic metastasis comprised 62% of patients, 18% had partial portal vein thrombosis, 85% were Child-Pugh A, 45% were hepatitis B and 30% were hepatitis C (Table 2).

SIRT treatment and complication rate. The majority of patients received a single administration of microspheres. The median activity administered was 1.3 GBq (range 0,8-2,0GBq), with predominantly whole-liver (45%) and right-lobe (38.5%) injections. The majority of whole-liver treatments were performed in a single session through one or more injections. The median hepato-pulmonary shunt was 12.7% (range, 1.2%-81%).

Common procedure-related adverse events did not occur in SIR-Spheres® patients. As summarized in Table 3. Ascites is a

Table 2. Baseline disease Characteristics

Characteristics, n (%)	MNC (N = 39)
Partial Portal vein thrombosis	
Yes	7 (17.9)
No	32 (82.1)
ECOG status	
0	16 (41.0)
1	23 (59.0)
Child-Pugh stage	
A	33 (84.6)
B	6 (15.4)
Not done	0
BCLC stage	
A	1 (2.6)
B	14 (35.9)
C	24 (61.5)
Not done	0
OKUDA stage	
I	36 (92.3)
II	3 (7.7)
III	0
Not done	0
TNM stage	
I	0
II	3 (7.7)
IIIA	28 (71.8)
IIIB	8 (20.5)

Table 1. Baseline patient Characteristics

Characteristics, n (%)	SIRT (N = 20)	Sorafenib (N = 19)	Total (N = 39)	p-value
Gender				0.7164*
Male	16 (80.0)	14 (73.7)	30 (76.9)	
Female	4 (20.0)	5 (26.3)	9 (23.1)	
Age (years)				0.1936*
N	20	19	39	
Mean (SD)	58.4 (8.79)	54.9 (7.67)	56.7 (8.35)	
Median (IQR)	60.0 (11.5)	57.0 (6.0)	57.0 (10.0)	
Min, Max	39,71	36,71	36,71	
Hepatitis B				0.5602
Positive	9 (45.0)	7 (36.8)	16 (41.0)	
Negative	4 (20.0)	7 (36.8)	11 (28.2)	
Hepatitis C				0.9203
Positive	6 (30.0)	6 (31.6)	12 (30.8)	
Negative	5 (25.0)	6 (31.6)	11 (28.2)	
Both hepatitis B and C				0.3011
Positive	2 (10.0)	0	2 (5.1)	
Negative	0	1 (5.3)	1 (2.6)	

Table 3. Summary of treatment emergent adverse events by treatment and grade

System organ class preferred term	SIRT (N = 16)		Sorafenib (N = 19)	
	Grade 1-2	Grade>=3	Grade 1-2	Grade>=3
Patients with at least one AE	14 (87.5)	9 (56.3)	18 (94.7)	9 (47.4)
Gastrointestinal disorders	1 (6.3)	0	6 (31.6)	1 (5.3)
Ascites	1 (6.3)	0	3 (15.8)	1 (5.3)
Diarrhea	0	0	1 (5.3)	0
Rectal hemorrhage	0	0	1 (5.3)	0
Vomiting	0	0	1 (5.3)	0
General disorders and administration site conditions	0	0	1 (5.3)	1 (5.3)
Disease progression	0	0	0	1 (5.3)
Fatigue	0	0	1 (5.3)	0
Infections and infestations	0	0	1 (5.3)	0
Sinusitis	0	0	1 (5.3)	0
Metabolism and nutrition disorders	0	0	2 (10.5)	1 (5.3)
Decreased appetite	0	0	1 (5.3)	0
Hyperglycemia	0	0	0	1 (5.3)
Hypoalbuminemia	0	0	1 (5.3)	0
Nervous system disorders	0	0	0	1 (5.3)
Encephalopathy	0	0	0	1 (5.3)
Skin and subcutaneous tissue disorders	0	0	3 (15.8)	0
Palmar-plantar erythrodysaesthesia syndrome	0	0	3 (15.8)	0
Vascular disorders	0	0	3 (15.8)	0
Hypertension	0	0	3 (15.8)	0

Table 4. Summary of investigations adverse events by treatment and grade

System organ class preferred term	SIRT (N = 16)		Sorafenib (N = 19)	
	Grade 1-2	Grade >=3	Grade 1-2	Grade>=3
Investigations	14 (87.5)	9 (56.3)	15 (78.9)	8 (42.1)
Alanine aminotransferase increased	10 (62.5)	2 (12.5)	7 (36.8)	4 (21.1)
Alphafetoprotein increased	2 (12.5)	1 (6.3)	4 (21.1)	0
Aspartate aminotransferase increased	9 (56.3)	5 (31.3)	10 (52.6)	4 (21.1)
Blood albumin decreased	7 (43.8)	0	4 (21.1)	1 (5.3)
Blood alkaline phosphatase increased	6 (37.5)	0	12 (63.2)	1 (5.3)
Blood bilirubin increased	5 (31.3)	6 (37.5)	9 (47.4)	4 (21.1)
Blood creatinine decreased	1 (6.3)	0	2 (10.5)	0
Blood creatinine increased	1 (6.3)	0	1 (5.3)	0
Platelet count decreased	6 (37.5)	0	4 (21.1)	0
White blood cell count decreased	3 (18.8)	0	0	0
White blood cell count increased	1 (6.3)	1 (6.3)	1 (5.3)	0

common adverse event in patients with advanced stage HCCand occurred in 1 patient in each treatment group (p>0.05).

Regarding liver-related events, elevated bilirubin (all grades) was recorded in 22.6% of patients at baseline, increasing to 37.5% of patients up to day 90, with a minority experiencing grade ≥4 events (5.5% up to day 90). A minor increase in the proportion of patients with grade >0 values for ALT, AST and platelet levels to day 90 was observed. There were no significant differences in the transitions in CTCAE for laboratory values among BCLC stages (Table 4).

Sorafenib treatment and complication rate. Adverse events that were reported for patients receiving sorafenib were predominantly grade 1 or 2 in severity and were gastrointestinal, constitutional and dermatologic in nature. The most frequently reported drug-related adverse events in patients treated with sorafenib were hypertension, hand-foot skin reaction, diarrhea alopecia, fatigue. Diarrhea, weight loss, hand-foot skin reaction, alopecia, and anorexia, occurred at higher frequency in the sorafenib group than in the SIRT group (Table 3).

Grade 3 and 4 laboratory abnormalities occurred in the Sorafenib treatment group, and the most common adverse events were increased ALT, AST and bilirubin (Table 4).

Treatment discontinuation due to adverse events in 4 of 19 patients (26.3%-5). Dose reductions due to adverse events were needed in 26.3% of 19 patients treated with sorafenib. The most common adverse events resulting in dose reductions were Hand Foot Syndrome (HFSR) (4 of 19 patients) and diarrhea (3 of 19 patients).

Discussion

The objective of this study was to assess the safety of sorafenib and SIRT treatment in Asia-Pacific patients with advanced hepatocellular carcinoma. From 2011 to 2016, we enrolled 39 Mongolian patients to the study and examined the adverse events of sorafenib and SIRT treatment. In this single center subgroup analysis of Mongolian patients which is part of a larger multi-center, randomized controlled trial, we showed no significant difference in adverse events difference between sorafenib and SIRT group (p-=0.0964, number of adverse events 83 in SIRT arm, 115 in Sorafenib arm).

The adverse events associated with sorafeinb treatment in patients with advanced hepatocellular carcinoma seen here were comparable with that reported in the SHARP trial. Sorafenib was generally well-tolerated and had manageable adverse events, with the most common drug-related adverse events including HFSR, diarrhea, alopecia, fatigue and hypertension. These adverse events were predominantly grade 1 or 2. The safety profiles for sorafenib in our study and in the SHARP trial were similar. However, there were specific differences of certain drug-related adverse events of any grade in the sorafenib groups of both studies, the incidence of HFSR (any grade) was higher in our study compared with the SHARP trial (26.2% vs 21.2%), whereas the incidence of diarrhea (21% vs. 39.1%) was lower in our study.

Overall, a low incidence of severe (grade>3) adverse events was observed with radio-embolization. The procedure itself was well tolerated, with mild-to-moderate nausea and/or vomiting, abdominal pain, and fever of limited duration occurring in less than one-third of patients. As would be expected in a population of patients with underlying chronic liver disease, many patients had grade 1 or 2 abnormal values in liver-associated parameters such as INR, bilirubin, platelets, and alanine aminotransferase prior to radio-embolization, and the majority experienced no change in grade at 3 months post treatment. In contrast with other liver function tests, grade 3 or higher increase in bilirubin was observed in 5% of patients.

A European study with similar inclusion criteria is currently ongoing comparing Sorafenib with SIRT in patients with advanced HCC, and could be used for meta-analysis in the future. The results from the SIRveNIB trial will impact clinical practice [20].

A definitive randomized controlled trial comparing the two most promising therapies in locally-advanced HCC should help determine the optimal treatment modality for HCC and may help identify populations that are best suited to either therapy. The study will also pave the way for future trials in combined modality therapies in HCC.

The study reports the results of 39 patients treated at the National Cancer center of Mongolia during 2011-2016. In our analysis of 39 patients, we were unable to detect a statistically significant difference in adverse effects between treatment groups, likely because there were insufficient number patients. Although we suspect with larger numbers of patients SIRT would be found to have fewer adverse events, we are unable to draw this conclusion with data available in our study. Also,

some patients withdrew voluntarily during the trial which further decreased the statistical of power of our study. Based on those lessons, in future studies we need to focus on recruiting larger numbers of patients and retaining patients once they are enrolled.

In conclusion, in our analysis of 39 patients, we were unable to detect a statistically significant difference in adverse effects between sorafenib and SIRT treatment groups, likely because there were insufficient number patients in our study.

Conflict of interest

The authors state no conflict of interest.

Acknowledgements

We express our deep appreciation to these organizations and people who helped us perform this study: Minister of Health Mongolia, National Cancer Center of Mongolia, Asia Pacific Hepatocellular Trial Group Singapore Clinical Research Institute, National Cancer Center of Singapore, Singapore General Hospital, SIRTEX Co.Ltd, Professor Pierce Kah-Hoe Chowof NCCS, other colleagues and administrators of hospitals, research co-workers, and all the staff who assisted us.

References

1. El-Serag HB, Rudolph KL. Hepatocellular carcinoma: Epidemiology and molecular carcinogenesis. Gastroenterology 2007; 132: 2557-76.
2. Llovet JM, Briux J. Review article: natural history and prognostic prediction of patients with hepatocellular carcinoma. Aliment Pharmacol Ther. 2003; 2: 98-102.
3. El-Serag Andrew C et all. Rising Incidence of Hepatocellular Carcinoma in the United States. N Engl J Med 1999; 340: 745-50.
4. McGlynn KA, Tsao L, Hsing AW, Devesa SS, Fraumeni JF, Jr. International trends and patterns of primary liver cancer. Int J Cancer 2001; 94: 290-6.
5. Llovet JM, Fuster J, Bruix J. The Barcelona approach: diagnosis, staging, and treatment of hepatocellular carcinoma. Liver Transpl 2004; 10: S115-20.
6. Hung H. Treatment modalities for hepatocellular carcinoma. Curr Cancer Drug Targets 2005; 5: 131-8.
7. Poon D, Anderson BO, Chen LT, Tanaka K, Lau WY, Van Cutsem E, et al. Management of hepatocellular carcinoma in Asia: consensus statement from the Asian Oncology Summit 2009. Lancet Oncol 2009; 10: 1111-8.
8. Pawarode A, Tangkijvanich P, Voravud N. Outcomes of primary hepatocellular carcinoma treatment: an 8-year experience with 368 patients in Thailand. J Gastroenterol Hepatol 2000; 15: 860-4.
9. Chow PK, Tai BC, Tan CK, Machin D, Win KM, Johnson PJ, et al. High-dose tamoxifen in the treatment of inoperable hepatocellular carcinoma: A multicenter randomized controlled trial. Hepatology 2002; 36: 1221-6.
10. Nowak AK, Chow PK, Findlay M. Systemic therapy for advanced hepatocellular carcinoma: a review. Eur J Cancer 2004; 40: 1474-84.
11. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008; 359: 378-90.
12. Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim J, Set al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009; 10: 25-34.
13. Sacco R, Mismas V, Marceglia S, Romano A, Giacomelli L, Bertini M, et al. Transarterial radio embolization for hepatocellular carcinoma: An update and perspectives. World J Gastroenterol. 2015; 21: 6518–25.
14. Sangro B, Carpanese L, Cianni R, Golfieri R, Gasparini D, Ezziddin S, et al. Survival after yttrium-90 resin microsphere radio embolization of hepatocellular carcinoma across Barcelona clinic liver cancer stages: a European evaluation. Hepatology. 2011; 54: 868-78.
15. Hwang YH, Choi JY, Kim S, Chung ES, Kim T, Koh SS, et al. Over-expression of c-raf-1 proto-oncogene in liver cirrhosis and hepatocellular carcinoma. Hepatol Res 2004; 29: 113–21.
16. Avila MA, Berasain C, Sangro B, Prieto J. New therapies for hepatocellular carcinoma. Oncogene. 2006; 26: 3866-84.
17. De La Coste, Romagnolo B, Billuart P, Renard CA, Buendia MA, Soubrane O et al. Somatic mutations of the beta-catenin gene are frequent in mouse and human hepatocellular carcinomas. Proc Natl Acad Sci USA. 1998; 95: 8847-51.

18. Viligrain V, Abdel-Rehim M, Silbert A, Ronot M, Lebtahi R, Castéra L, et al. Radio embolization with yttrium90 microspheres versus sorafenib for treatment of advanced hepatocellular carcinoma (SARAH): study protocol for a randomized controlled trial. Trials 2014; 15: 474.
19. Sanduijav R. Oncology. Ulaanbaatar, Mongolia: Edo publishing center; 2014, p 35-40, 279-295.
20. Lau WY, Kennedy AS, Kim YH. Patient selection and activity planning guide for selective internal radio therapy with ytrrium-90 resin microspheres. Int J Radiat Oncol Biol Phys 2012; 82: 401-7.