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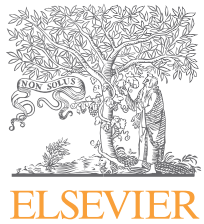

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Evolving clinical evidence for selective internal radiation therapy in hepatocellular carcinoma

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1. SIRT trials in Asia

1.1. Background

Hepatocellular carcinoma (HCC) is endemic in the Asia-Pacific region, affecting 10–20 per 100,000 of the population. Eighty percent of cases are inoperable at time of diagnosis and HCC is associated with a poor survival if left untreated.[1] For patients with metastatic disease, systemic therapy with sorafenib is the reference treatment.[2] However, for patients with inoperable local disease, both sorafenib and locoregional treatments are recommended in the absence of a recognised first-line treatment.[2] The current evidence indicates that for patients with intermediate (BCLC stage B) HCC, median overall survival is ~14 months with sorafenib[3,4] (level 1 evidence) and ~17 months with the locoregional treatment, selective internal radiation therapy (SIRT) (level 2 evidence).[5,6]

In the light of the encouraging data with SIRT in inoperable HCC, a number of prospective clinical trials are currently being conducted both in the Asia-Pacific as well as in Europe. The results of these trials will define the role of SIRT in the management of HCC.

1.2. SIRSA (AHCC05)

1.2.1. Rationale

Ablative therapy such as SIRT with yttrium-90 (^{90}Y) microspheres is associated with high tumour response, often resulting in complete or partial destruction of the tumour. Nevertheless, new lesions can arise within

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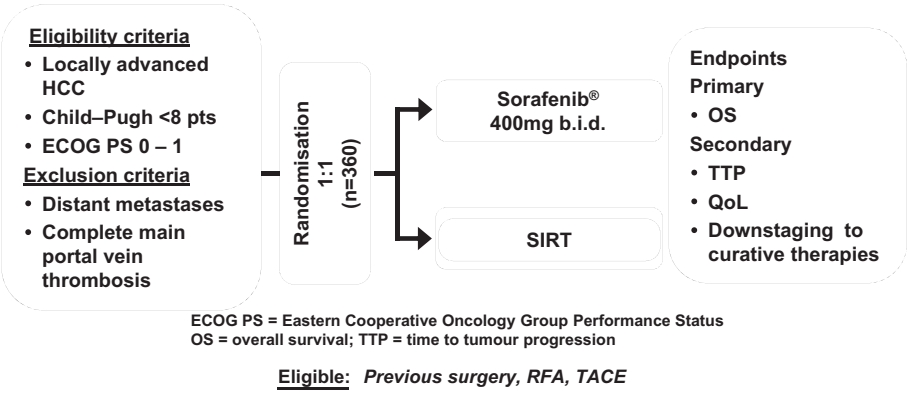

Fig. 1 – SIRveNIB (AHCC06) study design.

the liver or metastasise beyond the liver, which may be prevented by systemic molecular-pathway targeted therapy. It has been hypothesised that an efficacious locoregional therapy such as SIRT followed by a proven systemic therapy (such as sorafenib) may confer improved outcomes (in terms of tumour regression, better locoregional control in terms of time to tumour progression and improved survival) in advanced HCC. This hypothesis was tested by the Asia-Pacific HCC Trials Group in the SIRSA trial.

1.2.2. Study design

SIR-Spheres (^{90}Y-resin microspheres) plus **S**or**a**fenib (SIRSA) was a phase I/II study conducted at 4 centres in patients with non-resectable HCC in the Asia-Pacific region (Protocol AHCC05).[7] Sorafenib (400 mg b.i.d.) treatment was initiated 11–14 days after SIRT when only residual radiation levels were present (half-life of ^{90}Y is 64.1 hours). The primary endpoint was overall response rate, measured by RECIST 1.0.

1.2.3. Results

Two-thirds of patients were classified as advanced (Barcelona Clinic Liver Cancer [BCLC] stage C: 64.7%), with 57.9% of these patients presenting with major vascular invasion and 50.0% with extra-hepatic disease. Forty-four percent of patients had extensive disease burden with >50% liver involvement. Tumour response rate was 33.5% and the disease control rate was 79.5% (including 100% of patients with BCLC stage B and 68% of patients with BCLC stage C). Median time-to-disease progression was 9 months (95% CI 6.2–16.8 months) and overall survival was 20.6 months and 8.2 months in patients with BCLC stage B and stage C HCC, respectively. One patient was downstaged to receive transplantation and two others to receive radiofrequency ablation.

1.3. SIRveNIB (AHCC06)

1.3.1. Rationale

In early 2010, a second phase III trial was discussed by Asia-Pacific HCC Trials Group at the 5th General Meeting of the group held in Singapore. The study, designated SIRveNIB (Protocol AHCC06)[8] was designed to answer the following question, "For patients with inoperable locally advanced HCC with no metastases including those who have progressed following trans-arterial chemoembolisation (TACE) or RFA or those with inoperable recurrence after resection, should treatment be initiated with sorafenib or SIRT?"

1.3.2. Study design

SIRveNIB is an ongoing open-label, randomised-controlled phase III study in patients without extrahepatic metastases or complete main portal vein thrombosis (PVT) (branch PVT or incomplete main PVT are permitted) (Fig. 1). Eligible patients are randomised (1:1) to either sorafenib or SIRT with ^{90}Y-resin microspheres and are stratified by centre and the presence of PVT. The primary endpoint is overall survival defined as the time from the date of randomisation to the date of death due to any cause. Secondary endpoints include: time to progression, health-related quality of life (HRQoL), safety and downstaging to curative therapies. Currently, 105 of the planned 360 patients have been recruited from 26 centres. The first interim analysis is expected by the end of 2012.

2. SIRT trials in Europe

2.1. SORAMIC

2.1.1. Background

The clinical management of HCC requires a comprehensive, multidisciplinary approach. In early HCC, curative treatment can be achieved by local ablation, resection or liver transplantation. In intermediate stages of HCC, patients receive locoregional treatment with palliative intent (TACE or SIRT with ^{90}Y-radioembolisation). In patients with advanced disease, systemic therapy with sorafenib has the potential to prolong survival of patients and is standard of care in patients with preserved liver function.