Uitgangsvraag 8: Welke systemische therapie wordt aanbevolen bij HCC-patiënten?

Systematic reviews

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VII Results secondary and other outcomes	VII Critical appraisal of study quality
Zhang 2010 [1]	• SR + MA • Funding/CoI: no CoI to declare • Search date: 12/2008 • Databases: PubMed, ASCO and ESMO abstracts; reference lists & PDQR of clinical trials • Study designs: RCTs • N included studies: N=3	• Eligibility criteria: ○ Patients with advanced HCC	Sorafenib (N=496) vs. Placebo or other agent (N=428)	• Overall survival: HR 0.66 (95%CI 0.55-0.78, p<0.001) in favour of sorafenib	• Time-to-progression: HR 0.58 (95%CI 0.49-0.69, p<0.001) in favour of sorafenib • Toxicity: ○ Hand-foot syndrome: OR 13.43 (95%CI 3.53-71.47, p=0.002) in favour of placebo ○ Diarrhea: OR 2.41 (95%CI 0.99-5.88, p=0.05) in favour of placebo ○ No significant differences in other toxic events	Level of evidence: A1 • Simple search strategy • Study quality assessed, but not taken into account • Included studies: ○ Abou-Alfa 2009 (abstract) ○ Cheng 2009 (abstract) ○ Llovet 2008

Primaire studies

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VII Results secondary and other outcomes	VII Critical appraisal of study quality
Kudo 2011 [2]	• RCT • Funding/CoI: supported by Bayer HealthCare Pharmaceuticals and Onyx Pharmaceuticals; several authors received fees from Bayer or are employees of Bayer • Setting: 69 Japanese and 7 South-Korean centres • Sample size: N=458	• Eligibility criteria: ○ Patients with unresectable HCC ○ Child-Pugh A ○ At least 18y old ○ Sustained response 1-3 months after TACE ○ Maximum target lesion size of 70 mm ○ Maximum of 10 target lesions ○ Adequate bone marrow, liver, and renal function	Sorafenib 400 mg twice daily (N=229) vs. Placebo (N=229) All patients were treated with TACE (epirubicin, cisplatin, doxorubicin, mitomycin)	• 1-year overall survival: 94.6% vs. 94.1% • 2-year overall survival: 72.1% vs. 73.8% • HR of death: 1.06 (95%CI 0.69-1.64, p=0.79)	• Progression-free rates: ○ 3 mo: 65.0% vs. 58.7% ○ 6 mo: 45.7% vs. 33.5% • Safety: grade 3/4 ○ Hand-foot syndrome: 35% vs. 0% ○ Elevated lipase: 28% vs. 4% ○ Rash: 4% vs. 0%	Level of evidence: B • Unclear allocation concealment • Central evaluation of response • ITT analysis

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	• Duration: inclusion from 4/2006-7/2009	○ No extrahepatic metastases ○ No prior use of systemic agents for HCC • Group comparability: no obvious differences (Sorafenib vs. placebo) ○ Male: 76% vs. 73% ○ Median age: 69 vs. 70y ○ HCV: 61% vs. 65% ○ CR to TACE: 62% both				
Abou-Alfa 2010 [3]	• RCT • Funding/CoI: supported by research grant from Bayer; several authors received fees from Bayer • Setting: multinational multicentre study • Sample size: N=96 • Duration: inclusion from 4/2005-10/2006	• Eligibility criteria: ○ Patients with inoperable HCC ○ Child-Pugh A ○ Adequate bone marrow, liver, renal and cardiac function ○ No prior systemic treatments for HCC • Group comparability: no obvious differences (Sorafenib vs. placebo) ○ Male: 66% vs. 86% ○ Median age: 66 vs. 65y ○ HCV: 21% vs. 14%	Doxorubicin 60 mg/m² every 21 days for maximum of 360 mg/m² + sorafenib twice orally (N=47) vs. Doxorubicin 60 mg/m² every 21 days for maximum of 360 mg/m² + placebo twice orally (N=49)	• Median OS: 13.7 (95%CI 8.9-) vs. 6.5 months (4.5-9.9); HR 0.49 (0.3-0.8; p=0.006) in favour of sorafenib	• Median PFS: 6 (4.6-8.6) vs. 2.7 months (1.4-2.8); HR 0.54 (0.3-0.8; p=0.006) in favour of sorafenib • Toxicity: grade 3/4 ○ Hand-foot syndrome: 6.4% vs. 0%	Level of evidence: A2 • Concealed allocation • Blinded outcome assessors • ITT analysis
Cheng 2009 [4]	• RCT • Funding/CoI: supported by Bayer; several authors received fees from Bayer or are employees of Bayer • Setting: multicentre study, Asia-Pacific region • Sample size: N=226 • Duration: inclusion from 9/2005-1/2007	• Eligibility criteria: ○ Patients with unresectable or metastatic HCC ○ At least 18y old ○ Child-Pugh A ○ Adequate bone marrow, liver, renal function ○ No prior systemic treatments for HCC • Group comparability: no obvious differences	Sorafenib 400 mg orally twice daily (N=150) vs. Placebo (N=76)	• Median OS: 6.5 (95%CI 5.56-7.56) vs. 4.2 months (3.75-5.46); HR 0.68 (0.50-0.93; p=0.014) in favour of sorafenib • 6-month OS: 53.3% vs. 36.7%	• Toxicity: grade 3/4 ○ Hand-foot syndrome: 10.7% vs. 0% ○ Diarrhoea: 6% vs. 0%	Level of evidence: A2 • Concealed allocation • Double-blind study, although it is not clear who was blinded • ITT analysis

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		(Sorafenib vs. placebo) ○ Male: 85% vs. 87% ○ Median age: 51 vs. 52y ○ HCV: 16% vs. 3%				
Llovet 2008 [5]	• RCT • Funding/CoI: supported by Bayer HealthCare Pharmaceuticals–Onyx Pharmaceuticals • Setting: multinational multicentre study • Sample size: N=602 • Duration: inclusion from 3/2005-4/2006	• Eligibility criteria: ○ Patients with advanced-stage HCC (not eligible for or disease progression after surgical or locoregional therapies) ○ Child-Pugh A ○ Adequate bone marrow, liver, renal function ○ No prior systemic treatments for HCC • Group comparability: no obvious differences (Sorafenib vs. placebo) ○ Male: 87% vs. 87% ○ Median age: 65 vs. 66y ○ HCV: 29% vs. 27%	Sorafenib 400 mg orally twice daily (N=299) vs. Placebo (N=303)	• Median OS: 10.7 vs. 7.9 months; HR 0.69 (95%CI 0.55-0.87; p<0.001) in favour of sorafenib • 1-year OS: 44% vs. 33%	• Toxicity: grade 3/4 ○ Hand-foot syndrome: 8% vs. <1% ○ Diarrhoea: 8% vs. 2%	Level of evidence: A2 • Concealed allocation • Double-blind study, although it is not clear who was blinded • ITT analysis • Early termination of study

Abbreviations: 95%CI: 95% confidence intervals; CR: complete remission; HCC: hepatocellular carcinoma; HR: hazard ratio; ITT: intention-to-treat; MA: meta-analysis; OR: odds ratio; OS: overall survival; PFS: progression-free survival; RCT: randomized controlled trial; SR: systematic review; TACE: transarterial chemo-embolisation.