Additional ^{166}Ho-radioembolization after ^{177}Lu-DOATATE in patients with neuroendocrine tumor liver metastasis (HEPAR PluS): a single-centre, single-arm, open-label, phase 2 study

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Highlights

- Holmium-166 (Ho) radio-embolization (TARE)/Selective Internal Radiation Therapy (SIRT) is a safe and effective therapy in metastatic neuroendocrine tumor (mNET) patients with liver metastases after peptide receptor radionuclide therapy (PRRT)

Background

- In patients with neuroendocrine tumors (e.g. NET patients), metastatic disease is the most important prognostic factor for survival, and liver metastases are the most common type of metastasis
- Different systemic treatment options such as PRRT and somatostatin analogues are used as first line treatments for NET patients with unresectable disease, although there are differences in local guidelines
- Peptide receptor radionuclide therapy (PRRT) is approved as a first line treatment in many countries and results in a prolonged progression-free survival (PFS) and overall survival (OS), but a limited overall response of 18% at 3 months is reported from the pivotal trial[1]

Objective

- To investigate the efficacy in terms of hepatic objective response (according to RECIST 1.1) at 3 months and safety (according to CTCAE v4.03) of ^{166}Ho SIRT in mNET patients with liver metastasis

Methods

HEPAR Plus

- Prospective, open-label, non-randomized phase II study
- 30 patients with histologically proven grade 1 or 2 NET, of all origins, ECOG ≤ 2, and ≥ 3 measurable liver metastases according to RECIST 1.1 received ^{166}Ho SIRT (QuiremSpheres® & QuiremScout®) within 20 weeks after 4 cycles of PRRT (^{177}Lu-DOTATATE), regardless of progression after PRRT
- Extrahepatic disease was not an exclusion criteria

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Results

- ^{166}Ho SIRT induced an objective liver response (according to RECIST 1.1) of 43% and 47% at 3 and 6 months respectively (table 1)
- ^{166}Ho SIRT is safe and shows an acceptable toxicity profile according to CTCAE v.4.03 (table 2) with only temporary changes in QoL

RECIST 1.1	3 MONTHS		6 MONTHS	
	Liver specific response	Patient based response	Liver specific response	Patient based response
Complete response	0%	0%	0%	0%
Partial response	43%	40%	47%	33%
Stable response	50%	47%	37%	43%
Progressive response	7%	13%	13%	20%

Table 1.

RELATED TOXICITY	CTCAE GRADING			
	1-2	3	4	5
REILD				1 (3%)*
Abdominal pain	21 (68%)	3% (10%)		
Fatigue	18 (58%)	1 (3%)		
Nausea	19 (61%)	1 (3%)		
Vomiting	13 (42%)			
Malaise	8 (25%)			
(sub)febrile	4 (13%)			
Shivering	3 (10%)			
Oedema	2 (6%)			

Table 2.

* Patient with REILD had low liver cancer involvement (7%), a hypo vascular lesion and received methotrexate therapy (hepato-toxic treatment) for rheumatoid arthritis

CONCLUSION

The additional radiation boost of SIRT with ^{166}Ho-microspheres after PRRT has proven to be an effective treatment option by showing a high objective overall and liver specific response after 3 and 6 months, while showing an acceptable safety profile in mNET patients with liver metastasis.

Key Takeaways

- ^{166}Ho SIRT is:
  - an effective treatment option in terms of objective overall response rate and liver response rate in mNET patients with liver metastasis after PRRT
  - able to improve NET-related hormone symptoms not controlled by previous PRRT
  - safe after 4 cycles of PRRT showing only a temporary impact on the Quality of Life
  - could allow for a more personalized treatment approach for liver metastasis of mNET patients by allowing the selection of patients that will benefit from the additional radiation boost

1.Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 Trial of 177Lu-Dotatate for Midgut Neuroendocrine Tumors. N Engl J Med 2017; 376:125-35.

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