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Randomized Embolization Trial for NeuroEndocrine Tumors (RETNET)

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BACKGROUND

Transarterial bland and chemoembolization (TAE, TACE) have been employed for decades to treat liver-dominant neuroendocrine tumor (NET) metastases and are part of international guidelines without recommendation of a preferred technique. This international multicenter trial randomized patients to TAE, cTACE or DEB-TACE and evaluated efficacy, toxicities, and HRQoL.

METHODS

Patients with NET liver metastases of any histologic origin and grade that were progressive or symptomatic on somatostatin analog therapy or had >25% liver tumor burden were block randomized to bland embolization, lipiodol chemoembolization with a doxorubicin-based emulsion, or drug-eluting embolics with doxorubicin. Prior biliary intervention was an exclusion. Trial design was pragmatic with treatment according to each institutions' standard of care. Clinical, laboratory and imaging assessment was performed one month after completing liver-directed therapy, then every 3 months for 2 years. Toxicity was assessed by CTCAE and complications scored according to the SIR Classification. Blinded DSMB review was done at 10 and 30 patients per arm, then annually, with a 20% SAE rate as the stopping rule. Primary outcome was hepatic progression free survival (HPFS) by BICR. The study was powered for a hypothesized hazard ratio of 1.9 to detect a clinically meaningful difference.

RESULTS

The DEB-TACE arm was closed at the first safety review with an SAE rate of 40%. Between 2017-2022, 151 patients were randomized to TAE (n= 78) or cTACE (n=73) at 13 centers in North and South America and Europe. Primary sites of disease were midgut 54%, pancreas 36%, lung 4%, other/unknown 6%. Tumor grades 1/2/3/unknown were 36%, 56%, 3%, and 4%. 28% had prior liver resection or ablation. 76% had been on a somatostatin analog for an average of 3 years. Indications for embolization included tumor progression in 74%, high baseline tumor burden in 50%, symptom control in 44%, and downstaging in 6%. Baseline demographic and clinical parameters did not significantly differ between arms. SIR Class D-E complications occurred in 34 (44%) in the TAE arm and 21 (29%) in the cTACE arm. CTCAE G3-4 toxicities occurred in 42 (54%) in the TAE arm and 26 (36%) in the TACE arm. There was no statistically significant difference in HPFS by BICR for TAE vs cTACE, HR 1.40 [95% CI 0.80-2.46], p = 0.234 or in overall PFS, HR 1.43 [95% CI 0.90-2.26], p = 0.133.

CONCLUSIONS

DEB TACE has unacceptable toxicity in NETs. There is no significant difference in HPFS or PFS between TAE and cTACE. Serious toxicities and adverse events requiring elevated level of care occur more frequently with TAE.

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