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Initial Outcomes of Integrating Yttrium-90 Radioembolization with Capecitabine-Temozolomide for Grade 3 Liver-Dominant Metastatic Neuroendocrine Tumors

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BACKGROUND

Well-differentiated Grade 3 (G3) neuroendocrine tumors (NETs) are characterized by a high proliferative rate (Ki67 > 20%) with a prognosis between that of Grade 2 NETs and neuroendocrine carcinoma. Embolotherapy of G3 hepatic metastases has poor outcomes with median hepatic progression free survival (HPFS) of 4.9 months and overall survival (OS) of 9.3 months in a multicenter analysis. To improve these historical outcomes, an integrated protocol of radiosensitizing chemotherapy and radioembolization was developed.

METHODS

Patients with liver-dominant, well-differentiated G3 NET were treated with capecitabine 750 mg/m2 twice daily for 14 days followed by 14 days off. Temozolomide 200 mg/m2 daily x 5 days was given on days 10-14 of capecitabine (CapTem regimen). CapTem was given for a year or stopped at time of progression or intolerance if sooner. Simulation angiography with Tc99m-MAA SPECT was performed in the first cycle of CapTem. The dominant lobe was treated on day seven of the second cycle. Resin Y90 microspheres (SIR-Spheres) were administered using the body surface area method. For bilobar disease, the other lobe was treated in the third or fourth cycle. Clinical and laboratory assessment were done monthly and imaging every 3 months. PFS and OS were estimated by Kaplan-Meier method.

RESULTS

Seven patients had pancreatic NETs and one had an atypical lung carcinoid, with Ki67 21-70%. Two patients had extrahepatic metastasis. Median duration on CapTem was nine months (range 4-16 months). Thirteen radioembolizations were performed, with a median total dose per patient of 48 mCi (33-66 mCi). Grade three toxicities included ALT/AST elevation (n=2), hyperbilirubinemia (n=1), and anemia (n=1). There was one grade four thrombocytopenia, leading to CapTem hold and dose reduction. Median follow-up time from initiation of CapTem was 32 months. Four patients had partial response in the liver, two had stable disease, and two had progressive disease (ORR 50%). Median decrease in Chromogranin A was 58% (33-95%). All patients eventually developed intrahepatic progression. Median hepatic PFS was 9.3 months (2.8-40.5 months), and median extrahepatic PFS was 16.4 months. Multiple patients proceeded to alternative treatment regimens. Six patients died between 8-60 months from initiation of CapTem, with mOS of 30.8 months.

CONCLUSIONS

Integrated CapTemY90 chemotherapy and radioembolization showed acceptable toxicity, not greater than expected in this cohort of patients with G3 NETs. Hepatic and overall PFS suggest improved outcomes compared to that reported in the literature for G3 NETs treated with standard embolotherapy, noting that ours is a small cohort.

ABSTRACT ID 28641