Phase II Study of Sunitinib Malate Following Hepatic Artery Embolization for Patients with Metastatic Neuroendocrine Carcinomas

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Abstract:

Background: Neuroendocrine tumor (NETs) frequently metastasize to the liver. Hepatic artery embolization is an important therapeutic modality in patients with liver-predominant metastases. NETs are highly vascular and are known to express both VEGF and VEGFR. We hypothesize that administration of Sunitinib malate, a VEGFR inhibitor, following hepatic artery embolization will delay tumor revascularization and extend progression-free survival.

Methods: Patients with metastatic NETs to the liver underwent a series of selective arterial embolizations followed by Sunitinib (a week after each embolization and continued until disease progression or up to a maximum of 8 cycles). Radiographic response rates were evaluated according to RECIST criteria. PFS and OS were calculated using Kaplan-Meier methodology. Serum VEGF levels were drawn before and after the first embolization.

Results: 39 patients were enrolled. Primary tumor sites included the small-intestine (26), pancreas (9), rectum (2), lung (1) and unknown (1). The initial starting dose of sunitinib was 50mg; however due to poor tolerability, the starting dose was reduced to 37.5mg. Twenty eight patients (72%) had a partial radiographic response (PR), eight patients (20%) had stable disease, and three patients (8%) had progressive disease as best response. Median PFS was 18 months and the rate of 1-year PFS was 72%. Serum VEGF levels increased by an average of 51pg/ml (34%) after embolizations.

Conclusions: Hepatic artery embolization is a highly active treatment option for patients with metastatic NETs to the liver. Embolization stimulates release of VEGF into the circulation. Sunitinib, a VEGF inhibitor, can be safely administered following hepatic artery embolization at a daily dose of 37.5 mg. The high rates of PFS and OS associated with this sequence of therapies are encouraging.

Introduction:

- Hepatic arterial embolization (HAE) is a standard treatment option for liver-predominant metastatic NETs.
- NETs are highly vascular and express both VEGF its receptor
- Sunitinib malate is an multi-targeted receptor tyrosine kinase (RTK) inhibitor, that targets the VEGF receptor among other RTKs.
- Administration of sunitinib following hepatic arterial embolizations may prolong time to progression by inhibiting angiogenisis and tumor revascularization.

Methods:

- Series of 2-3 lobar hepatic arterial embolizations performed at 6 week intervals
- Sunitinib administered starting one week after each embolization and continued until tumor progression or a maximum of 12 months (figure 1).
- Initial dose of sunitinib: 50 mg qd days 1-28 every 42 days. Protocol amended to reduce starting dose to 37.5 mg due to excess toxicity.
- Radiographic response rates assessed by CT scans or MRIs and evaluated according to RECIST criteria.

Results:

- 39 patients treated (table 1)
- 28 patients (72%) had a partial radiographic response (PR), 8 patients (20%) had stable disease (SD) and 3 patients (8%) had progressive disease (PD) as best response (figure 2)
- Median PFS was 18 months
- Serum VEGF levels increased by an average of 51pg/ml (34%) after embolizations (figure 3)

Figure 1: Treatment schema

Table 1: Demographics and Tumor Characteristics

Median Age:	63 (range 40-75)
Gender:	21 females, 18 males
Primary Site:	26 small-intestine, 9 pancreas, 2 rectum, 1 lung, 1 unknown

Figure 2: Maximum percent tumor reduction

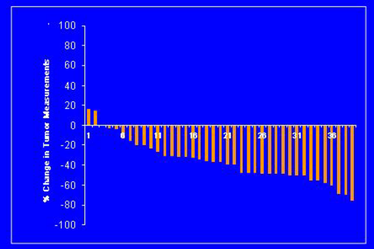
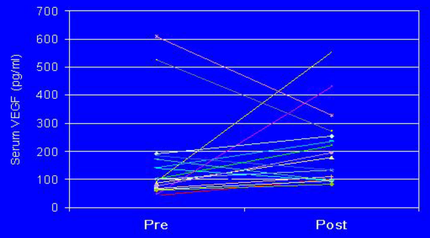


Figure 3: Changes in serum VEGF after first embolization



Conclusions:

1. Hepatic artery embolization is a highly active treatment option for patients with metastatic GEP-NETs.
2. Embolization stimulates release of VEGF into the circulation
3. Sunitinib, a VEGF inhibitor, can be safely administered following hepatic artery embolization at a daily dose of 37.5 mg
4. Median PFS is 18 months. The 2-year rate of OS is 78%.
5. The high rates of PFS and OS associated with this sequence of therapies are encouraging