



Markers of Angiogenesis Correlate with Response to Anti-Angiogenesis Therapy for Hepatocellular Carcinoma

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Background

- The incidence of Hepatocellular Carcinoma (HCC) in the United States is rising.
- Most patients are diagnosed at an advanced stage and thus are not candidates for curative treatment.
- Angiogenesis has been implicated in the development of HCC
- Copper is a required cofactor for angiogenesis
- Copper deficiency in rats has been shown to decrease tumor burden
- Tetrathiomolybdate (TM), a copper chelator, has been pioneered in our center for the treatment of Wilson disease
- TM had been used as an anti-angiogenesis therapy for patients with metastatic solid tumors, and shown to be safe and effective in stabilizing/reducing tumor burden in 7/18 patients

Aims

- To evaluate the effects of TM on HCC progression and tumor vascularity
- To correlate tumor response with changes in serum markers of angiogenesis
- To determine the safety of TM in patients with HCC

Methods

- Ongoing pilot study of patients with histology-proven HCC not amenable to resection, transplantation or local ablation
- No prior therapy for HCC
- Copper deficiency achieved by TM induction of 160 mg a day, maintenance dose titrated to keep ceruloplasmin (Cp) level between 5-15 mg/dl
- Intended duration of treatment - 12 months
- Dynamic MRI at baseline and every 3 months to evaluate tumor size and vascularity.
- Primary end-point - lack of tumor progression defined as no tumor increasing by more than 25% in the sum of the products of the longest diameter.
- Quantification of vascularity assessed by calculating relative signal intensity-time curves in the early (0-30 sec) and late (30 sec-5 min) phases of enhancement
- Serum collected every 3 months for markers of angiogenesis [vascular endothelial growth factor (VEGF), basic Fibroblast Growth Factor (bFGF), IL-6 and IL-8].

Results

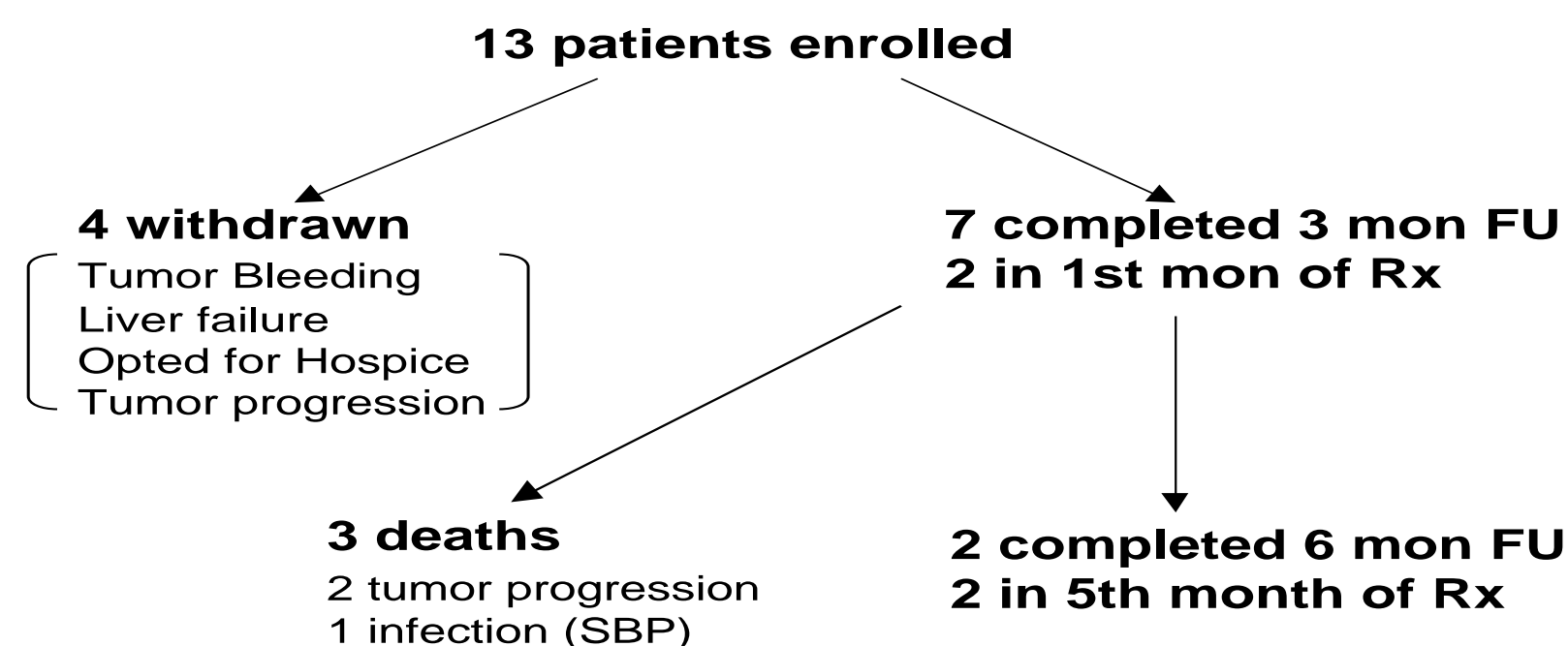


Table 1. Baseline characteristics of the patients enrolled in the study.

Age	60	(47-83)	Mean	
Sex	8M/5F		Tbili	1.3 mg/dl
Ethnicity	12 NHW/1AA		Alb	3.5 gm/dl
Diagnosis	9 HCV/3Cryptogenic/1Alcohol		INR	1.1
ECOG stage	7/5/1/		CTP	6
			Cp	29.8 mg/dl (19.5-45.7)
			AFP	304,419 ng/ml (4-3.1 mil)

Table 2. Tumor characteristics for all patients.

Diameter Largest Lesion (cm)	Number of Lesions	Portal Vein Invasion	Metastasis
8.9	1	Y	N
8.5	2	N	Y
4.8	1	Y	N
4.7	2	Y	N
16.8	1	N	N
15	1	Y	N
6.4	3	N	Y
7.5	1	N	N
5.9	1	Y	N
9	1	Y	N
11	1	N	N
6	1	Y	N

Results

- 4/7 patients had no tumor progression at 3 months
- 2/2 had no tumor progression at 6 months
- All patients with no tumor progression had decrease in tumor vascularity

Figure 1. Progressive decrease in tumor vascularity in patient 1

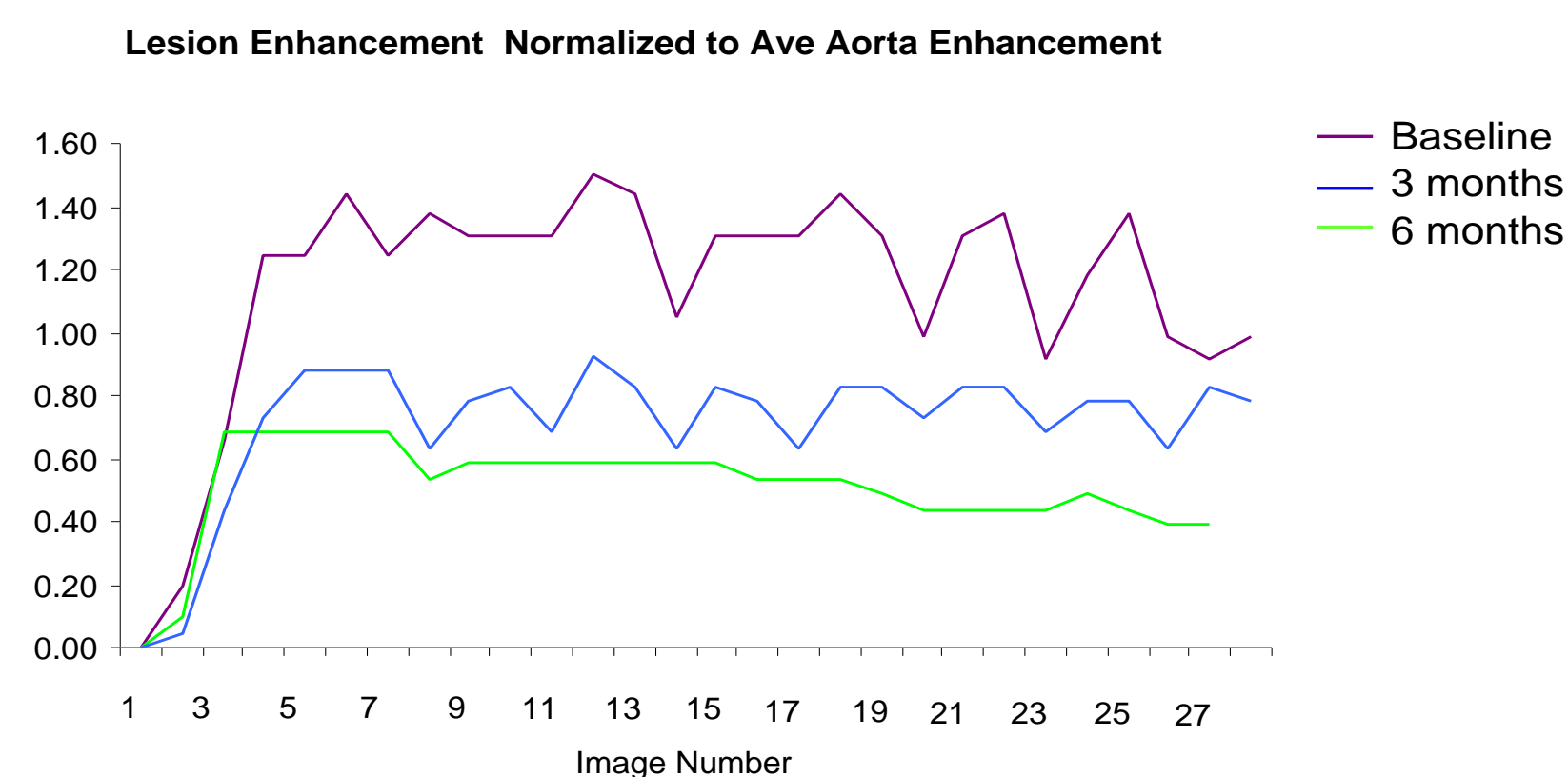
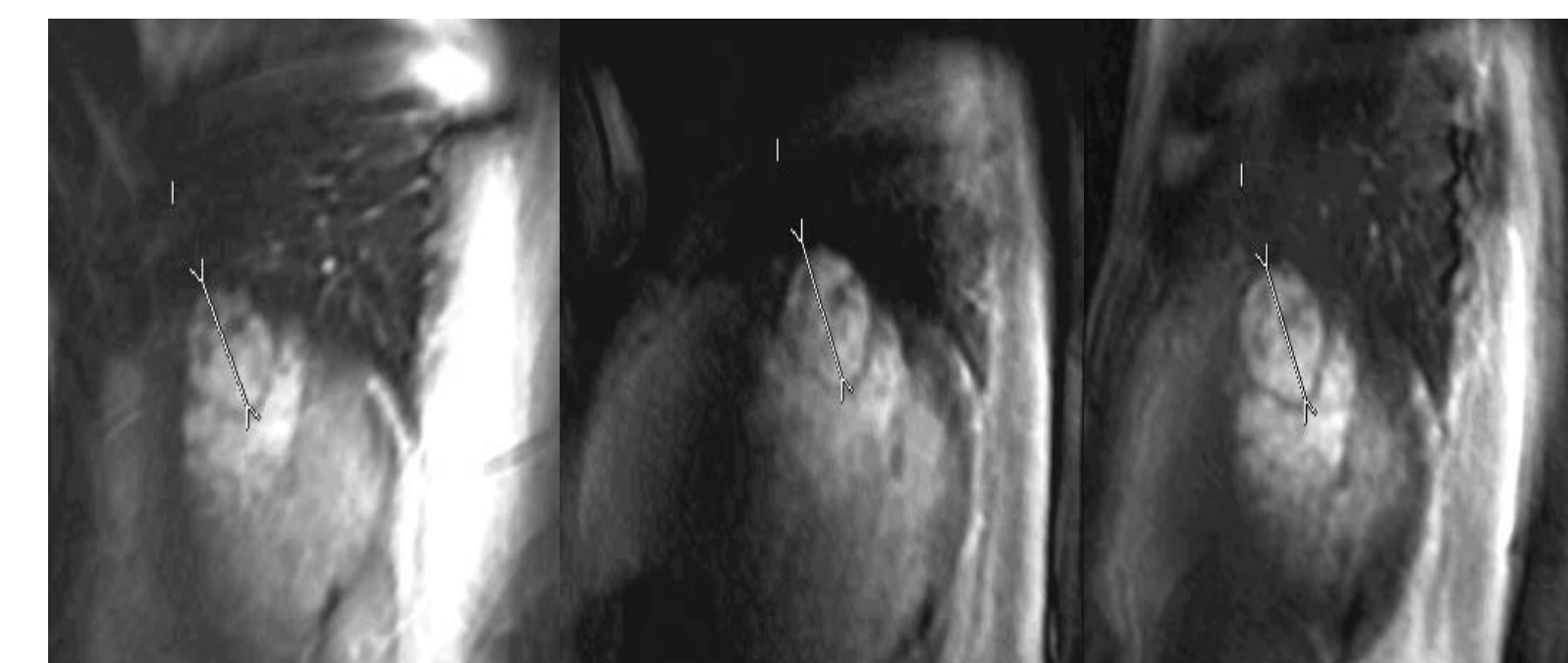


Figure 2. Serial MRI and AFP of patient 1



	Baseline	3 month	6 month
	4.79 cm	4.70 cm	4.31 cm
AFP	12.6	8	7.4

Figure 3. VEGF levels of the 7 patients that completed 3 months follow-up

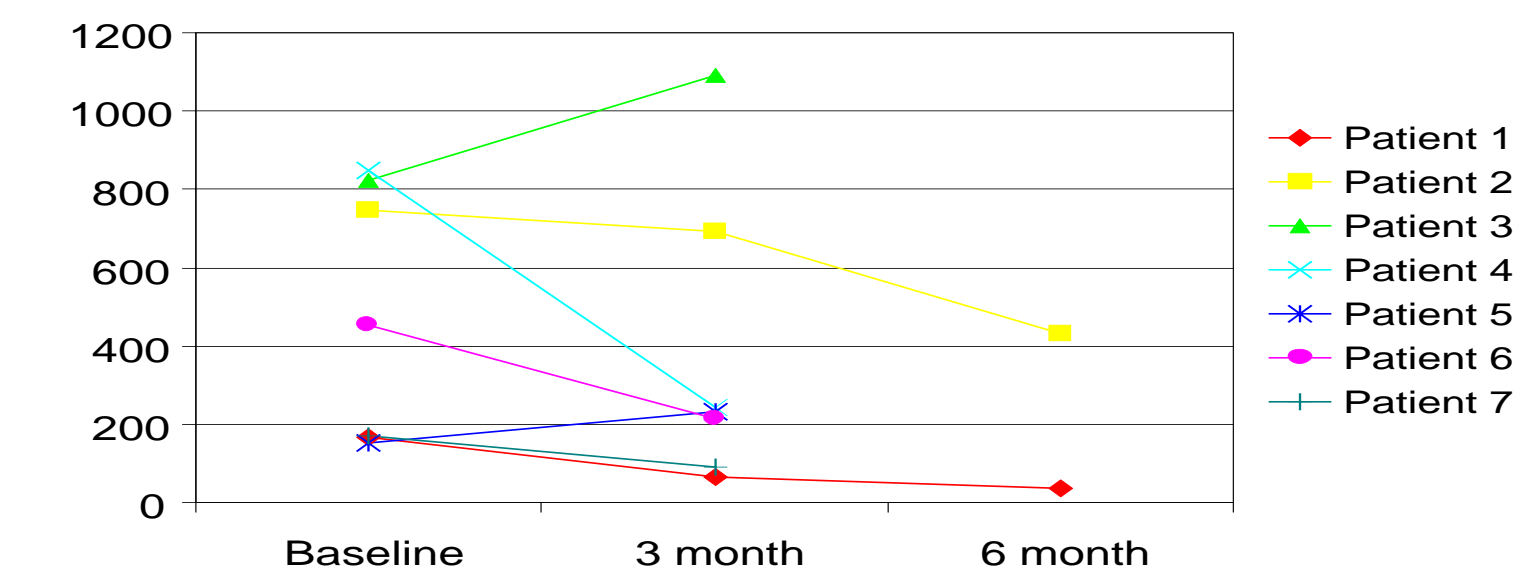
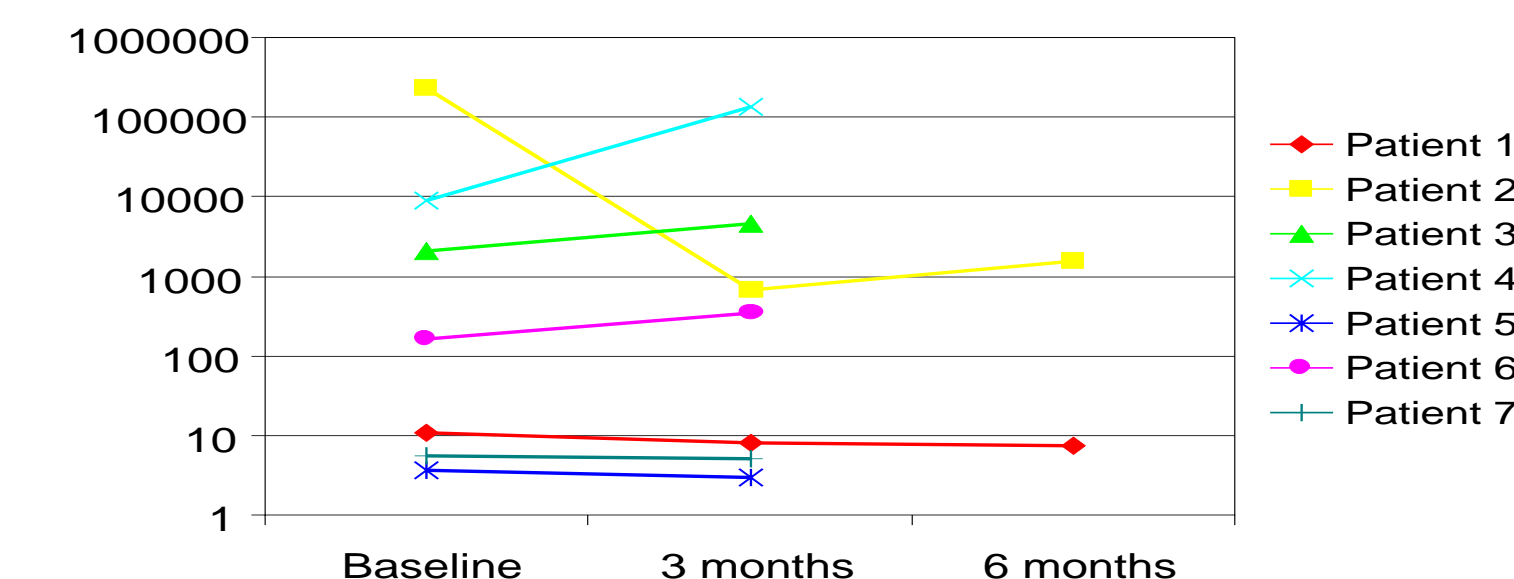


Figure 4. AFP levels of patients that completed 3 months follow up



Results

- bFGF, IL-6, and IL-8 decreased by >50% in patients with no tumor progression.
- Days of copper deficiency was important in predicting a response at 3 months: 76, 70, 72, and 78 in those with no tumor progression versus 21, 51 and 36 in those with tumor progression (p<.01)
- Treatment was well tolerated, apart from mild anemia which resolved with dose reduction.

Conclusion

- TM can prevent tumor progression in a subset of patients with advanced HCC
- TM appears to inhibit angiogenesis as shown by a decrease in serum markers of angiogenesis and a decrease in tumor vascularity
- TM is safe and well tolerated in patients with advanced HCC