Increased Dietary Folate Enhances the Effectiveness of Sorafenib Treatment in Renal Cell Carcinoma

KEITH ASHCRAFT PH.D.
DEPARTMENT OF UROLOGY
UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER SAN ANTONIO
Folate and Cancer—Finding a Healthy Balance

**Essential Vitamin B9 - Folate**
- One Carbon Pathway
- Supplementation in diet to combat neural tube defects

**Complex Role in Cancers**
- Low folate associated with increase risk of many cancers
- Higher folate increased risk of Prostate cancer *Curr Nutr Rep*. 2018; 7(3): 70–84

**Folates and Chemotherapy**
Folate and Renal Cell Cancer (RCC)

Inconclusive results from clinical studies
- Meta-Analysis shows no clear correlation with serum folate levels
- Folic acid supplementation showed 3% decrease of RCC

Drawbacks of studies
- Heterogeneity of population
- Dietary intake often determined through questionnaire

Sorafenib
- Tyrosine Kinase Inhibitor
- Targets angiogenesis
- Commonly used in hepatocellular carcinoma
How does dietary folate intake affect the growth of renal cell carcinoma?

Does dietary intervention sensitize tumors to Sorafenib?
Experimental Design: Dietary Intervention
Red Blood Cell Folate Levels

[Box plot diagram showing the effect of folate diets on RBC folate levels.]

* p<0.05

[Box plot diagram showing the effect of Sorafenib treatment on RBC folate levels.]
No effect of dietary folate intervention on tumor size
High folate diet sensitized tumors to Sorafenib
Decreased microvessel density in high folate diet + Sorafenib

![Graph showing CD34+ Microvessel Density](image1.png)

<table>
<thead>
<tr>
<th>Folate Diet (mg/kg)</th>
<th>Sorafenib</th>
<th># of CD34 Positive per Hotspot</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
<td>10</td>
</tr>
<tr>
<td>10</td>
<td>+</td>
<td>20</td>
</tr>
</tbody>
</table>

* * p<0.05

![Image showing CD34 staining](image2.png)

2mg/kg + Sorafenib

10mg/kg + Sorafenib
Conclusions

- Dietary folate intervention had no clear effect on tumor growth by itself
- Increased dietary folate sensitized tumors to Sorafenib treatment
- This corresponded with a decrease in microvessel density

Sorafenib is no longer widely used in RCC due to higher toxicity to similar chemotherapeutic drug Sunitinib. This study highlights a potential for folic acid to be used in conjunction with lower doses of Sorafenib to increase its efficacy while potentially limiting toxicity.
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Keith Ashcraft
ashcraft@uthscsa.edu