

The Effect of ANG-3777 on The Growth of c-MET-Expressing Human Tumor Cells in Immunocompromised Mice

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Background

Hepatocyte growth factor (HGF) is a renotropic factor that exerts significant cytoprotective and anti-apoptotic effects in renal epithelial cells.^{1,2} In the injured organs, HGF stimulates c-MET, leading to the activation of intracellular pathways involved in tissue repair.³ ANG-3777 is an HGF mimetic. In a Phase 2 study renal transplantation patients with signs of delayed graft function, a result of transplantation associated acute kidney injury, treatment with ANG-3777 (2mg/ml) showed renal function improvement relative to placebo up to 1 year post-transplantation.⁴ Uncontrolled activation of c-MET can play a role in oncogenesis and stimulate tumor growth. The objective of these studies were to assess the potential of ANG-3777 to stimulate tumor growth in human cell lines when implanted in immunocompromised mice.

Methods

Three c-MET-expressing human tumor cell lines were utilized in xenograft models; Glioma cells (U87-MG), Colon cancer cells (HT29), Pancreatic ductal carcinoma cells (SUIT-2).^{5,6,7} ANG-3777 was dissolved in DMSO at 2 mg/mL. DMSO was used as the vehicle control. A 50 μ l volume was administered to BALB/c nude mice. Overall survival (glioma transplant model) and tumor growth and weight (colon and pancreatic tumor xenograft models) were assessed.

Pancreatic ductal carcinoma cells: Human pancreatic ductal carcinoma cells SUIT-2 (obtained from the Japanese Collection of Research Bioresources [JCRB] Cell Bank) were used in the pancreatic tumor xenograft model. Cells (5 x 10⁶ cells in 100 μ l) were injected subcutaneously (SC) in the right hind flank of male BALB/c nude mice (n=20). Tumors were allowed to grow for 12 days, then animals were treated daily, 5 days a week, for 3 weeks with 2 mg/kg ANG-3777 or vehicle administered via IP injection. Tumor volume was measured twice weekly using dial calipers, and tumor weight was measured at sacrifice. Animals were sacrificed after the last dose administration.

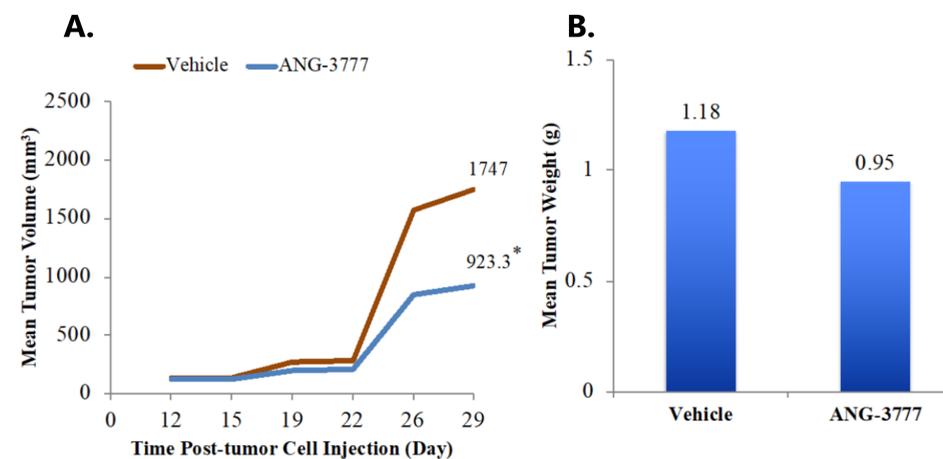
Glioma Cells: 2 independent studies were completed with human glioma cells U87-MG (obtained from American Type Culture Collection (ATCC) and were used in the glioma orthotopic model. Cells (2 x 10⁵ cells in 10 μ l) were injected intracranially into BALB/c nude mice (n=20;n=17). Tumors were allowed to grow for 7 days, then animals were treated daily until day 28 with 2 mg/kg ANG-3777 or vehicle administered via IP injection. Survival of the mice was monitored daily until all mice died.

Colon cancer cells: Human colon cancer cells HT29 (obtained from ATCC), were used in the colon tumor xenograft model. Cells (1 x 10⁶ cells in 100 μ l) were injected SC in the right hind flank of BALB/c nude mice (n=19). Tumors were allowed to grow for 7 days, then animals were treated daily until Day 27 with 2 mg/kg ANG-3777 or vehicle administered via IP injection. Tumor size was measured with dial calipers on Days 7, 12, 15, 19, 22, 27 and survival was recorded. Animals were sacrificed on Day 27 and tumor size and weight was recorded.

Results

Pancreatic Ductal Carcinoma Model: ANG-3777 did not have a statistically significant effect on the weight (Fig. 1B) of the pancreatic xenograft tumor. There was a statically significant reduction in the size of the tumor in the animals administered ANG-3777 (N=10) as compared to animals treated with the vehicle (N=10;Fig 1A).

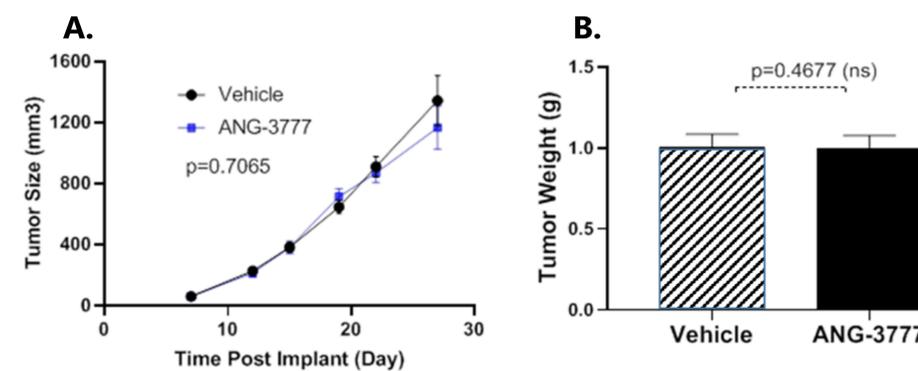
Figure 1. Effect of ANG-3777 on SUIT-2 Pancreatic Tumor



*p<0.01

Colon Cancer Model: ANG-3777 (N=9) did not have a statistically significant effect on the size (Fig. 2A) or weight (Fig. 2B) of the colon tumor xenograft tumor as compared to the animals treated with the vehicle (N=10).

Figure 2. Effect of ANG-3777 on HT29 Colon Tumor

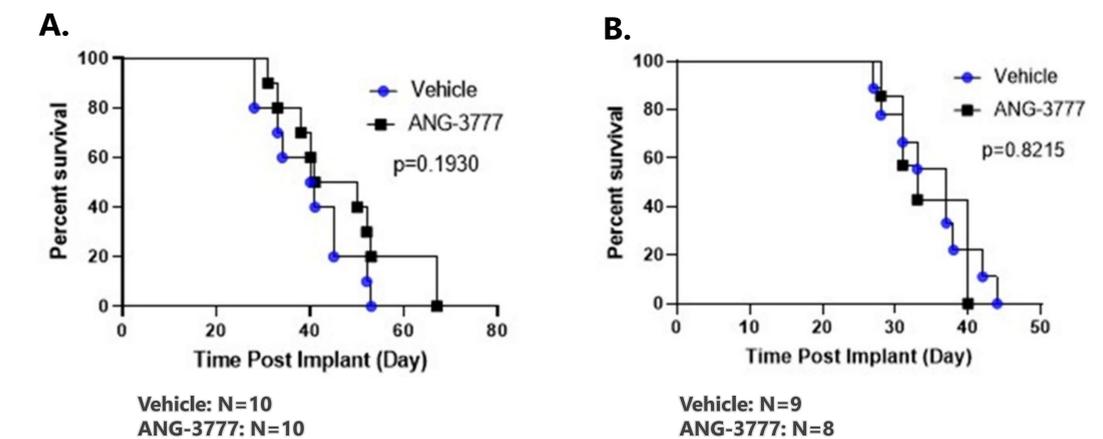


ns-not significant

Results (2)

Orthograft Glioma Model: In two independent studies of the glioma orthograft model, ANG-3777 did not have a statistically significant effect on the survival rate, as compared to the animals treated with the vehicle in each of study (Figure 3A and Figure 3B).

Figure 3. Effect of ANG-3777 on U87-MG Glioma



Conclusion

Exposure of ANG-3777 in BALB/c mice implanted with human tumor cells expressing c-MET was not associated with increased tumor volume or weight in pancreatic and colon tumor models and did not increase mortality in the glioma model.

These data from immunocompromised mouse models suggest that ANG-3777 does not increase or decrease tumorigenicity.

References

- de Souza Duraio M Jr, Razvickas CV, Goncalves EA, Okano IR, Camargo SM, Monte JC, dos Santos OF. The role of growth factors on renal tubular cells submitted to hypoxia and deprived of glucose. *Ren Fail.* 2003; 25:341-53.
- Igawa T, Matsumoto K, Kanda S, Saito Y, Nakamura T. Hepatocyte growth factor may function as a renotropic factor for regeneration in rats with acute renal injury. *Am J Physiol.* 1993;265:F61-69.
- Joannidis M, Spokes K, Nakamura T, Falletto D, Cantley L. Regional expression of hepatocyte growth factor/c-met in experimental renal hypertrophy and hyperplasia. *Am J Physiol. Renal Physiol* 1994; 25:F231-F236.
- Bromberg JS, Weir MR, Gaber AO, Yamin MA, Goldberg I, Mayne TJ, Cai W, Cooper M. Renal function improvement following ANG-3777 treatment in patients at high risk for delayed graft function after kidney transplantation. 2020; Online First.
- La B, Xia S, Abounader R, Laterra J. Targeting the c-Met pathway potentiates glioblastoma responses to gamma-radiation. *Clin Cancer Res.* 2005 Jun 15;11(12):4479-86.
- Wielenga VJ, van der Voort R, Taher TE, Smit L, Beuling EA, van Krimpen C, Spaargaren M, Pals ST. Expression of c-Met and heparan-sulfate proteoglycan forms of CD44 in colorectal cancer. *Am J Pathol.* 2000 Nov;157(5):1563-73.
- Maehara N, Matsumoto K, Kuba K, Mizumoto K, Tanaka M, Nakamura T. NK4, a four-kringle antagonist of HGF, inhibits spreading and invasion of human pancreatic cancer cells. *ChBr J Cancer.* 2001 Mar 23;84(6):864-73.