Methionine Aminopeptidase 2 Inhibition Is an Effective Treatment Strategy for Neuroblastaoma in Preclinical Models

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Abstract Tumor vascularity is correlated with an aggressive disease phenotype in neuroblastoma, suggesting that angiogenesis inhibitors may be a useful addition to current therapeutic strategies. We previously showed that the antiangiogenic compound TNP-470, an irreversible methionine aminopeptidase 2 (MetAP2) inhibitor, suppressed local and disseminated human neuroblastoma growth rates in murine models but had significant associated toxicity at the effective dose. We have recently shown that a novel, reversible MetAP2 inhibitor, A-357300, significantly inhibits CHP-134–derived neuroblastoma s.c. xenograft growth rate with a treatment-to-control (T/C) ratio at day 24 of 0.19 (P < 0.001) without toxicity. We now show that the combination of A-357300 with cyclophosphamide at the maximal tolerated dose sustained tumor regression with a T/C at day 48 of 0.16 (P < 0.001) in the CHP-134 xenograft model. A-357300 also significantly inhibited establishment and growth rate of hematogenous metastatic deposits following tail vein inoculation of CHP-134 cells and increased overall survival (P = 0.021). Lastly, A-357300 caused regression of established tumors in a genetically engineered murine model with progression-free survival in five of eight mice (P < 0.0001). There was no evidence of toxicity. These data show that MetAP2 may be an important molecular target for high-risk human neuroblastomas. We speculate that the growth inhibition may be through both tumor cell intrinsic and extrinsic (angiogenic) mechanisms. The potential for a wide therapeutic index may allow for treatment strategies that integrate MetAP2 inhibition with conventional cytotoxic compounds.

The prognosis for children with the embryonal malignancy neuroblastoma can vary widely depending upon both clinical features and tumor biology (1, 2). Although patients with localized disease may be successfully treated with surgery alone or minimal therapy, ∼50% of neuroblastoma patients present with metastatic disease and/or adverse tumor-specific biological features, such as MYCN amplification. Despite intensive multimodal therapy for these “high-risk” patients, cure rates remain <40% (3), and children who survive commonly experience significant long-term morbidity as a result of receiving dose-intensive therapy at a young age (4). Novel therapeutic approaches that will both improve patient survival and decrease treatment-related toxicity are clearly needed.

A growing body of evidence supports the concept of integrating antiangiogenic strategies into current treatment regimens for neuroblastoma. High-risk neuroblastomas are highly vascular and a strong association exists between the degree of vascularization and adverse prognostic variables. For example, intratumoral microvessel density is highly correlated with the presence of metastases at diagnosis, MYCN amplification, unfavorable histopathology, and survival probability (5). In addition, angiogenesis-related molecules seem to be differentially expressed in primary neuroblastomas in a pattern suggesting promotion of an angiogenic phenotype in high-risk tumors (6–11). Vascular inhibition strategies have proven successful in a variety of neuroblastoma preclinical models (12–17). Because current therapy for high-risk neuroblastoma may be at the tolerable limits for dose-intensive cytotoxicity (1, 18), antiangiogenic strategies are being pursued as potential adjuncts to current treatment regimens.

TNP-470 is a synthetic fumagillin analogue that suppresses endothelial cell growth and has been extensively studied as an antiangiogenic agent. It appears that vascular inhibition occurs through irreversible binding of methionine aminopeptidase 2 (MetAP2; ref. 19). MetAP2 is an ubiquitously expressed enzyme involved in both posttranscriptional and posttranslational protein processing, but the mechanisms by which inhibition of protein function inhibits angiogenesis has not been clearly defined (20). However, it is clear that TNP-470 has a potent
antiangiogenic effect and it has been shown to be active as a single agent in multiple preclinical models of neuroblastoma (12, 13, 16, 21, 22). Despite efficacy in murine models, objective responses were rarely observed in the clinic and neurologic toxicity was dose limiting (23, 24).

We recently reported on the structure-based design of a novel reversible MetAP2 inhibitor A-357300 (25). This compound potently inhibits endothelial cell growth in vitro and showed single-agent efficacy against a variety of human cancer xenografts, including neuroblastoma in vivo. This current study was designed to determine if MetAP2 is a valid molecular target in human neuroblastoma and to provide the preclinical rationale for further drug development.

**Materials and Methods**

**Drugs.** A-357300 was synthesized as previously described (26, 27) and was reconstituted in 0.2% hydroxypropyl methylcellulose and adjusted to pH 8.3 to yield a final working concentration of 10 mg/mL. A-357300 was used initially at a dose of 50 mg/kg s.c. twice daily 5 d/wk and was then decreased to 30 mg/kg s.c. twice daily 5 d/wk owing to improvements in the purity of the compound. Hydroxypropyl methylcellulose was used alone for placebo injections. Cyclophosphamide (Mead Johnson, Princeton, NJ) was constituted with sterile water (5 mg/mL) and administered at a total dose of 450 mg/kg, divided into three i.p. injections over 5 days.

**Cell line.** The CHP-134 cell line was derived from the primary tumor specimen of a patient with high-risk neuroblastoma characterized by MYCN amplification, chromosome 1p deletion, and unbalanced gain of 17q material (28, 29). Cells were grown in RPMI 1640 (Invitrogen Corporation, Carlsbad, CA) containing 10% fetal bovine serum (Hyclone, Logan, UT), 1% l-glutamine (Invitrogen), OPI (Invitrogen), penicillin and streptomycin, and 0.05% gentamicin (Invitrogen).

**Animal models and preclinical A-357300 trials.** Three different murine models of neuroblastoma were used in these studies, which were approved by the Animal Care and Use Committee of the Children’s Hospital of Philadelphia. First, 4- to 6-week-old athymic mice (nu/nu; National Cancer Institute, Frederick, MD) were used for a conventional s.c. xenograft model. A total of 10⁷ CHP-134 cells were pelleted and resuspended in 0.2 ml Matrigel (BD Biosciences, Bedford, MA). Cell suspensions were injected s.c. with a 26-gauge needle into the right flank. Tumor growth was observed within 10 to 14 days following inoculation in >95% of the animals. Tumor volume measurements were made by vernier caliper and were calculated using an ellipsoid formula (30). Animals with 0.4 cm³ tumors were enrolled on study and all were treated with cyclophosphamide. Mice underwent a balanced randomization before cyclophosphamide therapy based on tumor size and time because xenografting to A-357300 at 50 mg/kg s.c. twice daily 5 d/wk, or vehicle at the same volume and schedule. A-357300 therapy was initiated the day following the last dose of cyclophosphamide. Cyclophosphamide was given in 28 days cycles (two cycles total) and A-357300 (or vehicle) was interrupted during the second cycle. Tumor size was measured thrice weekly and treatment was discontinued for individual mice when tumor volume exceeded 3.0 cm³, at which point the mouse was sacrificed. Complete blood cell counts were obtained from four representative mice in each arm weekly for the duration of the study using a HemaVet Multispecies Hematology Analyzer (CDC Technologies, Oxford, CT).

Second, we used a tail vein injection model to study the effect of A-357300 on metastatic dissemination. Four- to eight-week old SCID-Beige mice were obtained from Charles River Laboratories, Inc. (Wilmington, MA), and each mouse received a tail vein injection of 10⁷ CHP134 cells. On the day after injection, mice were randomized to receive either single agent A-357300 at 50 mg/kg s.c. twice daily 5 d/wk, or vehicle at the same volume and schedule. Animals were observed daily until they showed signs of tumor progression (hunching, immobility, palpable mass) or survived to day 100.

Third, we studied the efficacy of A-357300 against spontaneously occurring neuroblastomas in a transgenic model. Mice in the 129X1/SVJ genetic background with the human MYCN oncogene overexpressed in the neural crest (generous gift from William Weiss, Department of Neurology, University of California, San Francisco, CA) develop neuroblastomas with high penetrance (31, 32). Tumors arise in the adrenal gland or abdominal paraspinal regions, show a histologic appearance very similar to human neuroblastoma, are locally aggressive, and often show microscopic evidence for metastatic disease (31). A-357300 was studied in an intervention design in these mice. A cohort of mice heterozygous for the transgene was screened weekly for palpable tumor. Mice found to have palpable tumors were randomized according to weight and date of birth 3:3:1 to A-357300 at 30 mg/kg s.c., twice daily, vehicle, or immediate sacrifice and necropsy. Animals were observed daily until they showed signs of tumor progression or survived to day 100.

**Pathology.** Complete necropsies were done in all SCID-Beige and transgenic mice to confirm tumor histology and to evaluate extent of disease. Organs and macroscopic tumors were fixed in 4% paraformaldehyde and embedded in paraffin for routine H&E staining. Bone marrow sections were prepared following decalcification with 10% hydrochloric acid. Neuroblastomas were considered to be well differentiated if background neuropil and cytodifferentiation toward ganglion cells could be identified with H&E staining. Tumor vascularity was assessed with the use of a biotinylated rabbit anti-rat, mouse adsorbed IgG antibody to CD31 (Vector Laboratories, Burlingame, CA), using standard methods.

**Statistical analyses.** Mixed-effects linear models were used to compare the rates of xenograft tumor growth over time between A-357300 and vehicle groups (33). Kaplan-Meier estimates were calculated, and progression-free survival distributions were compared using the log-rank test for both the tail vein and transgenic model experiments.

**Results**

**Combination of A-357300 with conventional-dose cyclophosphamide dramatically reduces xenograft growth rate.** We previously showed that A-357300 monotherapy significantly inhibited CHP-134 xenograft growth rate (25). To determine if A-357300 could provide additive efficacy with cytotoxic chemotherapy, without additive toxicity, we combined A-357300 with cyclophosphamide at the maximum tolerated dose. Treated animals showed tumor regression following cyclophosphamide that was sustained for the duration of the experiment [treatment-to-control ratio (T/C) at day 48 = 0.16, P < 0.001; Fig. 1]. Both treatment and control mice had mild weight loss following treatment with cyclophosphamide (mean 10% body weight loss for treatment mice and 8% for control mice comparing day 12 with day 0 weight), but both groups of mice regained weight by the end of the first cycle of cyclophosphamide. The treatment mice continued to have weights that were slightly less than at the start of therapy (mean 5% body weight difference comparing day 27 with day 0 weight), whereas the control mice regained weight so that their mean day 27 and day 0 weights were equal. Four mice in each group had serial complete blood counts measured and there was no discernable difference. Both groups showed WBC count nadirs at day 11, followed by identical recovery kinetics with normal WBC counts by day 25 (data not shown).

**Treatment with single-agent A-357300 prolongs survival in a murine model of disseminated hematogenous neuroblastoma metastasis.** On the day following a tail vein injection of
10^7 CHP-134 cells, SCID-Beige mice were randomized to receive either A-357300 or vehicle. In vehicle-treated animals, death due to progressive disease at multiple organ sites occurred at a median of 41 days (Table 1). In contrast, treatment with A-357300 inhibited growth of the metastatic deposits and significantly increased progression-free survival (P = 0.021; Fig. 2). Metastases were macroscopically visible in the brain, liver, adrenal medulla, bone marrow, and ovaries in mice that died from progressive disease. One animal in the A-357300 treatment group died of infection on day 35 without any sign of tumor, and one animal each in the drug and placebo groups had an incidental finding of fungal pneumonia at the time of necropsy. The single mouse that survived to day 100 in the placebo arm showed subclinical disease in the bone marrow. In the A-357300-treated animals, two of six animals surviving to day 100 showed no evidence for disease on gross and microscopic examination. The remaining four mice showed subclinical metastatic deposits in the brain, adrenal medulla, bone marrow, and/or liver. A-357300–treated mice had normal weight gain and no overt drug-related toxicity was observed.

**A-357300 monotherapy of established transgenic neuroblastomas induces complete responses.** Transgenic mice expressing the human MYCN oncogene were examined daily after weaning. When abdominal tumors became palpable, mice were randomized according to weight and date of birth to receive either A-357300, 30 mg/kg s.c. twice daily, vehicle, or immediate sacrifice and necropsy in a ratio of 3:3:1. Each of the mice that were immediately sacrificed showed a well-established paraspinous or adrenal neuroblastoma (median weight 1.4 g; range 1.2-2.3 g). Mean age at initiation of therapy was 72.7 days for the 11 mice in the treatment arm, and 73.8 days for the 12 mice in the control arm. All of the mice treated with vehicle died of progressive tumor burden with a mean progression free survival of 14 days (Fig. 3). In contrast, only three mice treated with A-357300 died of tumor progression (P < 0.0001; Fig. 4; Table 2). At day 100 of treatment, five mice in the treatment arm remained alive and were sacrificed. Necropsies were done on all mice, and specimens from all but two control mice were submitted for microscopic evaluation. Macroscopic tumor was observed at necropsy in 12 of 12 (100%) control mice and 5 of 11 treatment mice (45%). Of the 10 control tumors observed histologically, 8 were poorly differentiated, 1 was well differentiated, and 1 showed a mixed tumor type.

**Table 1. Tumor burden and necropsy results from mice inoculated with CHP-134 neuroblastoma cells via tail vein at day 0 and treated with placebo or A-357300**

<table>
<thead>
<tr>
<th>Mouse</th>
<th>Day of death</th>
<th>Ovary</th>
<th>Adrenal medulla</th>
<th>Brain</th>
<th>Liver</th>
<th>Bone marrow</th>
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<td>-</td>
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<td>-</td>
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<tr>
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<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
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<td>+</td>
<td>+</td>
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</tr>
<tr>
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<td>+</td>
<td>+</td>
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<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviation: NA, tissues are not available for gross examination.
* Negative on gross examination, microscopic examination not done.
\* Necropsy not done.
\† Animals surviving to day 100 were sacrificed and necropsied.
\* Subarachnoid spread also noted.
\* Fungal pneumonia noted on necropsy.
\* Presumed infection, no tumor detected.

**Fig. 2.** A-357300 significantly inhibits establishment and growth rate of hematogenous metastatic deposits in a metastatic neuroblastoma model. Following i.v. inoculation of CHP-134 neuroblastoma cells, mice received either A-357300 (50 mg/kg twice a day) or vehicle. Kaplan-Meier survival curve shows significantly improved progression-free survival in treated mice. Only one of eight mice treated with A-357300 showed signs of progressive disease by day 100, whereas six of seven mice in the placebo arm died from progressive metastatic disease at a median of 41 days (log rank P = 0.021).
node metastases were seen in 7 of 10 (70%) of control mice but histologically, but only 1 of 11 (9%) treatment mice. Lymph invasion) were seen in 8 of 10 (80%) control mice examined vascular basement membranes and without parenchymal metastases were identified in any control or treatment mice. Other was small (0.3 cm) and was found when the mouse was intramuscular abscess that was likely the cause of death; the necrosis. Two of the tumors were found incidentally. One of micewith palpable abdominal tumors were randomized to receive other was small (0.3 cm) and was found when the mouse was sacrificed at day 100. Representative histologic sections from control and treatment mice are shown in Fig. 4. No solid organ tumors seen on necropsy in treatment mice; however, this was most likely attributable to the enzymatic active site. Although it has been shown to have significant antitumor activity in clinical trials for cervical, breast, and lung cancers, its dose-limiting neurotoxicity and short halflife have prevented its incorporation into further clinical trials and treatment regimes (44–47). A-357300 is a reversible MetAP2 inhibitor recently synthesized and evaluated in preclinical models (25). Studies to date have shown that A-357300 inhibits angiogenesis both in vitro and in vivo by specifically and potently inhibiting MetAP2. It has also been shown to suppress growth of both endothelial and some primary tumor cells in culture. Finally, single-agent A-357300 has been shown to inhibit tumor growth in xenograft models of human neuroblastoma, fibrosarcoma, and breast cancer.

To further evaluate the preclinical efficacy of A-357300 against neuroblastoma, we tested the drug in several murine models. First, we investigated the potential for A-357300 to enhance the activity of conventional cytotoxic therapy. These experiments were designed to recapitulate the clinical scenario of providing cycles of cytotoxic agents at or near the maximum tolerated dose, and explored the potential of bridging the gap between cycles with an angiogenic agent. Similar to the situation observed clinically (48), the degree of tumor volume reduction diminished with subsequent cycles of chemotherapy and mice in the placebo arm all were euthanized because of progressive disease. However, A-357300 clearly prevented tumor regrowth between chemotherapy cycles. Mice treated with A-357300 had decreased weight compared with vehicle-treated mice; however, this was most likely attributable to differences in tumor size rather than drug-related toxicity, and there was no evidence of hematopoietic toxicity. These data catalyzing the removal of the NH2-terminal methionine from the majority of cellular proteins, MetAP2 is thought to carry out this methionine processing for only a small number of nascent proteins (38). Studies to date support the hypothesis that MetAP2 may play a central role in endothelial cell proliferation and tumorigenesis. First, although MetAP2 is expressed in all mammalian tissues, concentrations of the enzyme have been shown to be higher in tumors compared with normal tissue (39–41), including in neuroblastoma. Second, various methods of MetAP2 inhibition have been shown to induce G1 cell cycle arrest and cytostasis of tumor cells in vitro or to reduce tumor growth in vivo (25, 39, 42). Finally, the association between MetAP2 and tumor progression has been strengthened by a recent report demonstrating the physical interaction between MetAP2 and the metastasis-associated protein S100A4 and the effects of this association on endothelial cell growth and tumor metastasis (34). On the other hand, small interfering RNA–mediated depletion of MetAP2 in endothelial cells did not affect the cell proliferation or growth inhibition induced by the natural products fumagillin or bengamide in vitro (43). Additional work focused on determining the direct biochemical consequences of MetAP2 enzymatic inhibition on solid tumor cell and stomal (endothelial cell) proliferation and survival is clearly warranted.

A-357300 is a novel reversible MetAP2 inhibitor developed following early experience with the anticancer agent TNP-470. Previously evaluated in several phase I clinical trials, TNP-470 irreversibly inhibits MetAP2 activity by forming a covalent bond to the enzymatic active site. Although it has been shown to have significant antitumor activity in clinical trials for cervical, breast, and lung cancers, its dose-limiting neurotoxicity and short half-life have prevented its incorporation into further clinical trials and treatment regimes (44–47). A-357300 is a reversible MetAP2 inhibitor recently synthesized and evaluated in preclinical models (25). Studies to date have shown that A-357300 inhibits angiogenesis both in vitro and in vivo by specifically and potently inhibiting MetAP2. It has also been shown to suppress growth of both endothelial and some primary tumor cells in culture. Finally, single-agent A-357300 has been shown to inhibit tumor growth in xenograft models of human neuroblastoma, fibrosarcoma, and breast cancer.

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Discussion

The continued high morbidity and mortality observed in high-risk neuroblastoma patients underscores the need for novel therapeutic strategies. Optimal agents will exploit the unique biological features of this disease and will provide a wide therapeutic index. Our current understanding of the vascular biology of neuroblastoma supports the incorporation of angiogenesis inhibitors into neuroblastoma treatment regimens and indicates that these agents may provide antitumor efficacy without significant host toxicity.

The intracellular metalloenzyme MetAP2 has emerged as a potential target for antiangiogenic therapy in neuroblastoma. This enzyme is one of two methionine aminopeptidases responsible for protein stability and posttranslational modifications (34–37). Whereas MetAP1 is the dominant protein in

![Fig. 3. A-357300 significantly prolongs survival in a transgenic mouse model of neuroblastoma.](image-url)
suggest that A-357300 or other antiangiogenic agents may be useful between cycles of induction chemotherapy.

We next tested the hypothesis that MetAP2 inhibition with A-357300 would inhibit establishment of metastatic deposits and prolong animal survival in a tail vein inoculation model. Each animal in the placebo group showed extensive disseminated disease, typically in the adrenal medulla, brain, and liver. In contrast, the treatment group showed a dramatically reduced tumor burden (Table 1). Two of six mice that were sacrificed at the end of the study (day 100) had no evidence of disease. The one mouse in the treatment arm that died early because of infection in this immune compromised host also had no evident tumor. The remainder of the treatment mice did have demonstrable tumor at necropsy, but, in general, the tumor burden was much less than in the placebo-treated mice. Taken together, these data suggest that A-357300 inhibits the establishment of metastatic deposits and, thus, may prevent hematogenous dissemination of disease.

Finally, A-357300 treatment was studied in a genetically engineered murine model of human neuroblastoma. Tumors in these mice are morphologically and genetically similar to human neuroblastomas, show a robust vasculature, and, thus, provide an outstanding model for developmental therapeutics (31, 32). In this intervention design study, mice with easily palpable abdominal tumors were randomized to receive single-agent A-357300 or vehicle. Importantly, four mice were sacrificed when a tumor was palpated instead of enrollment on study to prove that the technician’s documentation of palpable tumor was verifiable on necropsy. All four mice sacrificed at the time of initial tumor palpation had a tumor discovered at necropsy. Mean progression-free survival time was only 14 days for mice treated with placebo following tumor palpation. In contrast, mice treated with A-357300 had a mean progression-free duration of 84 days, with five of eight mice surviving progression free to day 100. All control mice showed large abdominal tumors with lymph node and intravascular pulmonary metastases present in 70% and 80% of control mice, respectively. In contrast, four mice were disease-free and one mouse had a small tumor at day 100 in the A-357300 treatment arm. Two of the four disease-free mice showed periadrenal calcifications, histopathologic evidence strongly suggestive of complete tumor regression. In this study design where the antiangiogenic agent was initiated at the time of detection of a palpable tumor, A-357300 seems to be a potently effective antineuroblastoma agent that can regress established tumors.

In summary, A-357300 seems to exert potent antiangiogenic and direct antitumor effects via specific inhibition of the
Targeting MetAP2 in Neuroblastoma

MetAP2. Data presented here provides additional support to previously published studies, demonstrating that A-357300 inhibits neuroblastoma growth in preclinical mouse models and may do so without the dose-limiting neurologic toxicities seen with irreversible MetAP2 inhibitors. Specifically, we have shown that A-357300 enhances the efficacy of cyclophosphamide, limits the establishment of metastatic disease, and induces tumor regression as a single agent when given in a physiologically appropriate neuroblastoma model. Taken as a whole, these results support further preclinical development of MetAP2 inhibitors for neuroblastoma and suggest that A-357300 would be a rational addition to current neuroblastoma treatment strategies for patients with aggressive disease. Clinical trials to evaluate newer MetAP2 inhibition strategies should be pursued.

References
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