The Vascular Disrupting Agent STA-9584 Exhibits Potent Antitumor Activity by Selectively Targeting Microvasculature at Both the Center and Periphery of Tumors

Kevin P. Foley, Dan Zhou, Chris Borella, Yaming Wu, Mei Zhang, Jun Jiang, Hao Li, Jim Sang, Tim Korbut, Josephine Ye, Xuemei Zhang, James Barsoum, and Andrew J. Sonderfan

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Abstract

Vascular disrupting agents (VDAs) are an emerging class of therapeutics targeting the existing vascular network of solid tumors. However, their clinical progression has been hampered because of limited single-agent efficacy, primarily caused by the persistence of surviving cells at the well perfused "viable rim" of tumors, which allows rapid tumor regrowth to occur. In addition, off-target adverse events, including cardiovascular toxicities, underscore a need for compounds with improved safety profiles. Here, we characterize the mechanism of action, antitumor efficacy, and cardiovascular safety profile of (*S*)-2-amino-*N*-(2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)phenyl)-3-phenylpropanamide hydrochloride (STA-9584), a novel tubulin-binding VDA. In vitro, 2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)aniline (STA-9122) (active metabolite of STA-9584) displayed increased potency relative to other tubulin-binding agents and was highly cytotoxic to tumor cells. STA-9584 induced significant tumor regressions in prostate and breast xenograft models in vivo and, in an aggressive syngeneic model, demonstrated superior tumor growth inhibition and a positive therapeutic index relative to combretastatin A-4 phosphate (CA4P). It is noteworthy that histological analysis revealed that STA-9584 disrupted microvasculature at both the center and periphery of tumors. Compared with CA4P, STA-9584 induced a 73% increase in central necrotic area, 77% decrease in microvasculature, and 7-fold increase in tumor cell apoptosis in the remaining viable rim 24 h post-treatment. Ultrasound imaging confirmed that STA-9584 rapidly and efficiently blocked blood flow in highly perfused tumor regions. Moreover, cardiovascular effects were evaluated in the Langendorff assay and telemetered dogs, and cardiovascular toxicity was not predicted to be dose-limiting. This bioactivity profile distinguishes STA-9584 from the combretastatin class and identifies the compound as a promising new therapeutic VDA candidate.

Footnotes

- Article, publication date, and citation information can be found at http://jpet.aspetjournals.org. http://dx.doi.org/10.1124/jpet.112.196873.
- ↵[S] The online version of this article (http://jpet.aspetjournals.org) contains supplemental material.
- ABBREVIATIONS:

VDA
vascular disrupting agent

CA4
combretastatin A-4

CA4P
CA4 phosphate

ASA404
5,6-dimethylxanthenone-4 acetic acid

MTD
maximal tolerated dose

NSCLC
non–small-cell lung cancer

TUNEL
terminal deoxynucleotidyl transferase dUTP nick-end labeling

HUVEC
human umbilical vein endothelial cell

DMSO
dimethyl sulfoxide

PBMC
peripheral blood mononuclear cell

SCID
severe combined immunodeficient

LVP_{dev}
developed left ventricular pressure

QTc
corrected QT interval

T/C
treated/control

Oxi4503
[3-methoxy-2-phosphonatooxy-6-[(Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl] phosphate

AVE8062
(2S)-2-amino-3-hydroxy-N-[2-methoxy-5-[(Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl]propanamide

AVE8063
(Z)-2-methoxy-5-(3,4,5-trimethoxystyryl)aniline

MN-029
methyl-[5-[[4-[[(2S)-2-aminopropanoyl]amino]phenyl]sulfanyl]-1H-benzimidazol-2-yl]carbamate monohydrochloride

ZD6126
N-acetylcochinol-O-phosphate

NPI-2358
(3Z,6Z)-3-[(5-tert-butyl-1H-imidazol-4-yl)methylene]-6-(phenylmethylene)-2,5-piperazinedione

CYT997
N-ethyl-N′-[2-methoxy-4-[5-methyl-4-[[(1S)-1-(3-pyridinyl)butyl]amino]-2-pyrimidinyl]phenyl]urea

STA-9122
2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)aniline

STA-9584
(S)-2-amino-N-(2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)phenyl)-3-phenylpropanamide hydrochloride

ZD6216
(5S)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5H-dibenzo[a,c]cyclohepten-3yl dihydrogenphosphate.

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