



Investigational Drug Shows Promise as Treatment for Overexposure to Common Cancer Chemotherapy

Emergency Use of Vistonuridine as Antidote to 5-FU Overdose to be Reported at ASCO

FDA Grants Orphan-Drug Status

GAITHERSBURG, Md.—May 14, 2009 -- The emergency use of an investigational drug has yielded promising results in reducing the potentially fatal side effects of the widely used cancer chemotherapy 5-fluorouracil (5-FU), according to clinical data that will be reported June 1 at the annual meeting of the American Society of Clinical Oncology (ASCO) in Orlando.¹

The investigational drug, vistonuridine, was used to treat patients who had been accidentally overdosed with 5-FU and whose physicians had requested the drug for emergency use. The National Institutes of Health estimate that 275,000 patients in the United States undergo 5-FU therapy annually and that 1,300 die of 5-FU overexposure, which can result from either overdoses or poor drug clearance.²

Currently, no antidote for 5-FU overexposure is approved by regulatory authorities. Vistonuridine is being developed by Wellstat Therapeutics Corporation.

The presentation at ASCO will report on 17 cases of 5-FU overdose for which Wellstat supplied vistonuridine under emergency-use Investigational New Drug provisions of the Food and Drug Administration (FDA).³ Vistonuridine was flown or couriered to physicians immediately following their requests. The emergency treatment commenced as rapidly as possible after 5-FU overdose (within 8 to 96 hours), depending on the timing of the request to Wellstat and the location of the treatment site.

All 17 of the vistonuridine-treated patients recovered, even though a fatal outcome for at least 13 of the patients would have been predicted by the dose and rate of 5-FU administration. Preclinical and clinical data indicate that earlier treatment with vistonuridine resulted in milder toxicity than did later treatment.



In marked contrast to these observations were data from a review of 13 other cases in which patients *did not* receive vistonuridine but had 5-FU overdoses of a similar magnitude to those in the vistonuridine-treated group.⁴ The cases were reported by the Institute for Safe Medication Practices Canada, the FDA MAUDE database, and other sources.⁵ In this comparator group, 11 of 13 cases resulted in a fatal outcome.

“Because no antidote for 5-FU overexposure is approved today, we have been responding to emergency requests for vistonuridine,” said Michael Bamat, Vice President, Research and Development, Wellstat. “The data support the life-saving potential of this agent in cases of 5-FU overdose, and we plan to seek regulatory approval in the US and Europe.”

Orphan-drug status

Orphan-drug designation of vistonuridine as an antidote in the treatment of 5-FU poisoning was granted by the FDA on May 1. A similar designation, which provides incentives to bring to market drugs for rare medical conditions, was recommended on April 2 to the European Commission by a committee of the European Medicines Agency (EMA).

5-FU, in use as a cancer drug for decades, is an important mainstay of various treatment regimens for solid tumors including those of the colon, stomach, esophagus, breast, and head and neck. The drug is most commonly administered by infusion pump at or near what is considered the maximum tolerated dose. Yet many patients do not receive optimally effective treatment with 5-FU because of concerns about dose-limiting toxicity and individual variation in 5-FU metabolism.⁶

Expected side effects of 5-FU include myelosuppression (a reduction in white-blood-cell counts and thus increased risk of infection), diarrhea, nausea, vomiting, and mucositis (a painful inflammation of the mucous membranes lining the digestive tract). Overexposure to 5-FU can lead to severe myelosuppression, gastrointestinal hemorrhage, septic shock, multiple organ failure, and death.

The incidence of 5-FU overexposure is low though difficult to quantify. Overexposure may result despite careful selection of patients and adjustment of dose, both because the effective dose must often be close to a toxic dose and because patients vary in their capacity to break down 5-FU and eliminate it from the body.⁷ Instances of accidental overdose may result from infusion-pump problems and dose-calculation errors.



About vistonuridine

Vistonuridine is an orally active prodrug of uridine, meaning that vistonuridine is converted to uridine in the body. Once vistonuridine is converted to uridine, it reduces the incorporation of 5-FU metabolites into the genetic material of non-cancerous cells. Because of the poor bioavailability of oral uridine, however, and because of complications associated with infusion of uridine, uridine itself is not a clinically viable treatment for 5-FU overexposure. Vistonuridine delivers about eight-fold more uridine into the bloodstream than does oral administration of uridine.

Wellstat is also investigating the potential use of vistonuridine when given following 5-FU administration to achieve higher, more effective doses of 5-FU while preserving an acceptable margin of safety.

Vistonuridine does not have marketing approval for any indication.

About Wellstat Therapeutics Corporation

Wellstat Therapeutics Corporation, a privately held biopharmaceutical company in Gaithersburg, Maryland, is dedicated to the discovery, development, and commercialization of innovative therapeutics that expand the frontier of modern medicine. The company focuses on oncology, metabolic disorders including diabetes, and neurometabolic disorders.

Wellstat Therapeutics is part of the Wellstat group of companies, which are developing therapeutics, vaccines, and point-of-care diagnostics.

Notes to editors:

¹von Borstel R, O'Neil JD, Bamat MK. Vistonuridine: An orally administered, life-saving antidote for 5FU overdose.

²Federal Register/Vol. 73, No. 129, July 3, 2008.

³The emergency use of an investigational drug requires an Investigational New Drug (IND) submission to the Food and Drug Administration. The usual procedure is to contact the manufacturer and determine whether the drug can be made available under an IND.



⁴Whether or not an antidote for 5-FU overexposure is available, various types of supportive care may be provided, such as growth factors to stimulate blood-cell production and antibiotics.

⁵Institute for Safe Medication Practices Canada. Fluorouracil Incident Root Cause Analysis. May 22, 2007. <http://www.cancerboard.ab.ca/NR/rdonlyres/2FB61BC4-70CA-4E58-BDE1-1E54797BA47D/0/FluorouracilIncidentMay2007.pdf>.

⁶Gamelin E, Delva R, Jacob J, et al. Fluorouracil Dose Adjustment Based on Pharmacokinetic Follow-Up Compared With Conventional Dosage: Results of a Multicenter Randomized Trial of Patients With Metastatic Colorectal Cancer. (2008) J. Clin. Oncol. 26:2099-2105.

⁷A genetic variation in some patients results in deficient levels of an enzyme (DPD, or dihydropyrimidine dehydrogenase) essential for 5-FU metabolism.

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