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SPECIAL POINTS OF INTEREST

*New CDC
recommendation for
2009 - 2010:*

*Vaccinate all children
ages 6 months – 18
years of age for
seasonal influenza*

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Vistonuridine: An Antidote for Fluorouracil

Note: Vistonuridine was designated as an Orphan Drug in the United States on May 1, 2009.

5-FU is a mainstay of various chemotherapy protocols. It is used for treatment of solid tumors, including breast, colorectal, gastrointestinal, and head and neck cancers. It is commonly given intravenously. Topical forms of the drug are also available for treatment of malignant keratoses of the skin. 5-FU distributes widely throughout the body tissues and crosses the blood-brain barrier in significant amounts. It exhibits nonlinear kinetics such that as the dose increases the elimination rate decreases, bioavailability is higher, and the elimination half-life is longer.

When used intravenously, 5-FU is typically dosed in amounts approaching the maximum tolerated dose. Adverse drug effects can include severe bone marrow depression with abnormal lab results and symptoms of fever, sore throat, and/or abnormal bleeding. Stomatitis may be an early sign of severe toxicity. Life-threatening and sometimes fatal enterocolitis, dehydration, and diarrhea have occurred when high-dose 5-FU is given in combination with leucovorin, especially in elderly patients. GI bleeding, esophagitis, and proctitis have also been reported. Hepatic arterial infusions of fluorouracil have been associated with hepatitis, cholestatic jaundice, and biliary sclerosis, as well as mucositis and diarrhea. Octreotide has been reported to be useful in the treatment of severe 5-FU-induced diarrhea.

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Influenza: Seasonal and H1N1 Flu Vaccines

The 2009-2010 flu season is approaching. An extra challenge is the outbreak of H1N1 influenza ("swine flu") that appeared earlier in the year, causing outbreaks of disease on a completely different schedule than what is normally considered to be the season for influenza in the United States. Unfortunately, it will not be possible this year to have one single vaccine that can protect a person from both the seasonal flu and the H1N1 flu.

Influenza viruses change constantly. The normal seasonal flu vaccine is developed every year based on influenza strains found in other countries where the flu season occurs earlier than in the United States. Since it cannot be certain how the flu viruses will spread or mutate over several months and different parts of the world, the annual vaccine that is available in this country has a certain amount of guesswork involved in its development, and it may or may not be a good match for the flu viruses that actually reach the U.S. population in a certain year. Even if the vaccine is not a very good match, it still provides some protection.

There are two types of seasonal influenza virus vaccine. The injectable product is made from killed viruses. It can be used in patients as young as 6 months of age. Patients who are pregnant may receive the injectable flu vaccine. The intranasal form is made from live but weakened (attenuated) influenza viruses. It is sprayed into the nostrils. The intranasal vaccine is approved for persons aged 2 through 49 years of age, who are not pregnant and who do not have certain chronic health conditions. The Centers for Disease Control (CDC) has fact sheets available for both kinds of seasonal flu vaccine on their website at <http://www.cdc.gov/vaccines/pubs/vis/default.htm#flu>. These documents include information about the vaccine as well as guidelines for who should be vaccinated.

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Palmar-plantar erythrodysesthesia (hand and foot syndrome) occurs in roughly 24 – 40% of patients who receive an extended continuous IV infusion of fluorouracil. With high-dose continuous infusions, this toxicity can be dose-limiting. Hand and foot syndrome is characterized by a tingling sensation of the hands and feet when holding objects or walking which may progress over several days. The palms and soles become symmetrically swollen with erythema and tenderness of the ends of the fingers and toes, possibly accompanied by desquamation. The syndrome will resolve over 5 – 7 days following cessation of 5-FU therapy. Pyridoxine has been reported to ameliorate the syndrome but its safety and effectiveness have not been established.

In a presentation at the 2009 Annual Meeting of the American Society of Clinical Oncology (ASCO), researchers described outcomes for 17 patients with 5-FU toxicity that were treated with vistonuridine as an antidote. Patients received vistonuridine beginning 8 to 96 hours after a 5-FU overdose, in an amount of 10 grams every 6 hours for 20 doses. All 17 overdose patients treated with vistonuridine recovered fully. Earlier administration of the antidote resulted in less severe toxicity. In contrast, all 11 of the literature-reported cases of 5-FU overdose for which an outcome of death would have been predicted died from the overdose despite receiving supportive care.

Vistonuridine is converted to uridine in the body. Uridine is a specific antidote for 5-FU toxicity. Once converted, it reduces the incorporation of 5-FU metabolites into the genetic material of non-cancerous cells. Oral uridine has poor bioavailability and is not given intravenously. Vistonuridine is an orally-administered prodrug of uridine that delivers about 8-fold more uridine than administration of uridine itself.

Toxicity from 5-FU overdose is serious, debilitating, and life-threatening. The administration of vistonuridine may allow patients with 5-FU toxicity to recover, even in cases where a lethal outcome otherwise would have been expected.

References:

Wellstat Therapeutics Corporation: call 443-831-5626 for further information or to order the drug.

Gold Standard, Incl., Clinical Pharmacology: Fluorouracil. Accessed on August 14, 2009.

(Influenza Vaccines: continued from page 1)

The vaccine that is being developed for the H1N1 influenza virus is completely different than the seasonal flu vaccine. This new vaccine is currently in a testing phase, after which it will be available to the general public. The current estimate for its release is for some time in October, but that could change depending on the results of clinical trials and manufacturing issues. This vaccine will be specific for the H1N1 virus and will not have any effect on preventing seasonal flu. Recommendations for the H1N1 vaccination can be found on the CDC website at www.cdc.gov.

The CDC issues guidelines on who should receive various vaccinations. The guidelines for 2009-2010 include a change in strategy to include vaccination of all children for the seasonal flu, as follows:

- **Annual vaccination of all children aged 6 months – 18 years should begin as soon as the 2009-2010 influenza vaccine is available.**
- Annual vaccination of all children aged 6 months – 4 years (59 months) and older children with conditions that place them at increased risk for complications from influenza should continue to be a primary focus of vaccination efforts as providers and programs transition to routinely vaccinating all children.

It is important to advise patients that they cannot get influenza from a flu vaccine. Many people mistakenly believe that a flu vaccination causes them to have the flu. What patients should understand is that the vaccine only protects against the viruses for which it was developed, so a person could have flu-like symptoms from a different organism such as a cold virus. In addition, some mild aches and pains can be associated with any vaccination due to the vaccine's mechanism for building immunity, but these symptoms should be mild and only last a few days.

Vaccination for seasonal flu should be done as soon as possible, but can be done at any time before or during the regular flu season. It takes up to 2 weeks for protection to fully develop after vaccination. However, if a person has not yet had a seasonal flu vaccination and the H1N1 vaccine is available, both vaccinations can be done on the same day.

Reference: Centers for Disease Control website information, accessed August 14, 2009 including <http://www.cdc.gov/flu/professionals/acip/primarychanges.htm>