

New Anticancer Agents Have Distinctive Toxicities

BY BRUCE JANCIN
Denver Bureau

AMSTERDAM — The highly promising new class of investigational anticancer agents known as cytotoxic T-lymphocyte antigen 4 blockers has a characteristic group of side effects of special interest to dermatologists, gastroenterologists, and endocrinologists, Dr. Alexander M.M. Eggermont said at the 11th World Congress on Cancers of the Skin.

Two fully human monoclonal antibodies to CTLA4 are making major waves in oncology circles because of their efficacy in early clinical trials for the treatment of advanced melanoma, a disease which has seen discouragingly little therapeutic progress in the last 3 decades.

But it is apparent that this impressive efficacy comes at the price of what are known in the field as immune-related adverse events, or IRAEs, affecting mainly the dermatologic, gastrointestinal, and en-

docrinologic domains. The CTLA4 blockers have moved into an extensive program of large phase III clinical trials, so an increasing number of physicians will be confronted with IRAEs, which require prompt diagnosis and intervention, noted Dr. Eggermont, professor and head of surgical oncology at Erasmus University Medical Center, Rotterdam, and president-elect of the Federation of European Cancer Societies.

CTLA4 is expressed on T cells, where it functions as a fundamental negative reg-

ulator of T-cell activation. CTLA4 blockade essentially allows T-cell proliferation, enabling the patient's immune system to mount a more vigorous, prolonged, and effective anticancer response—and, in a sizable minority of cases, trigger IRAEs.

"If you have subclinical autoimmune disease, you may be propelled into clinical disease manifestations because the hand brake is off your T-cell populations," Dr. Eggermont explained at the congress, cosponsored by the Skin Cancer Foundation and Erasmus University.

Dermatologic IRAEs take the form of an array of rashes, vitiligo, and pruritic conditions involving specific T-cell infiltrates

BRIEF SUMMARY

R_x Only **ADOXA[®] 150 mg** DOXYCYCLINE CAPSULES

INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of doxycycline capsules and other antibacterial drugs, doxycycline capsules should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

In severe acne, doxycycline may be useful adjunctive therapy.

CONTRAINDICATIONS

This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.

WARNINGS

THE USE OF DRUGS OF THE TETRACYCLINE CLASS DURING TOOTH DEVELOPMENT (LAST HALF OF PREGNANCY, INFANCY, AND CHILDHOOD TO THE AGE OF 8 YEARS) MAY CAUSE PERMANENT DISCOLORATION OF THE TEETH (YELLOW-GRAY-BROWN).

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including doxycycline, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

This adverse reaction is more common during long-term use of the drugs but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported.

All tetracyclines form a stable calcium complex in any bone-forming tissue. A decrease in the fetal growth rate has been observed in premature infants given oral tetracycline in doses of 25 mg/kg every six hours. This reaction was shown to be reversible when the drug was discontinued.

Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues, and can have toxic effects on the developing fetus (often related to retardation of skeletal development). Evidence of embryo toxicity has been noted in animals treated early in pregnancy. If any tetracycline is used during pregnancy or if the patient becomes pregnant while taking these drugs, the patient should be apprised of the potential hazard to the fetus.

The antianabolic action of the tetracyclines may cause an increase in BUN. Studies to date indicate that this does not occur with the use of doxycycline in patients with impaired renal function.

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Patients apt to be exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur with tetracycline drugs, and treatment should be discontinued at the first evidence of skin erythema.

PRECAUTIONS

General: Prescribing doxycycline capsules in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

As with other antibiotic preparations, use of this drug may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, the antibiotic should be discontinued and appropriate therapy instituted.

Bulging fontanels in infants and benign intracranial hypertension in adults have been reported in individuals receiving tetracyclines. These conditions disappeared when the drug was discontinued.

Information for Patients: Patients should be counseled that antibacterial drugs, including doxycycline capsules should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When doxycycline capsules are prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by doxycycline capsules or other antibacterial drugs in the future.

Laboratory Tests: In long-term therapy, periodic laboratory evaluations of organ systems, including hematopoietic, renal, and hepatic studies should be performed.

Drug Interactions: Because tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracyclines in conjunction with penicillin.

Absorption of tetracyclines is impaired by antacids containing aluminum, calcium, or magnesium, and iron-containing preparations.

Barbiturates, carbamazepine, and phenytoin decrease the half-life of doxycycline.

The concurrent use of tetracycline and methoxyflurane has been reported to result in fatal renal toxicity. Concurrent use of tetracycline may render oral contraceptives less effective.

Drug/Laboratory Test Interactions: False elevations of urinary catecholamine levels may occur due to interference with the fluorescence test.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals to evaluate the carcinogenic potential of doxycycline have not been conducted.

However, there has been evidence of oncogenic activity in rats in studies with related antibiotics, oxytetracycline (adrenal and pituitary tumors) and minocycline (thyroid tumors). Likewise, although mutagenicity studies of doxycycline have not been conducted, positive results in *in vitro* mammalian cell assays have been reported for related antibiotics (tetracycline, oxytetracycline). Doxycycline administered orally at dosage levels as high as 250 mg/kg/day had no apparent effect on the fertility of female rats. Effect on male fertility has not been studied.

Pregnancy: Teratogenic Effects. Pregnancy Category D: There are no adequate and well-controlled studies on the use of doxycycline in pregnant women, first trimester exposure. There are no human data available to assess the effects of long-term therapy of doxycycline in pregnant women such as that proposed for treatment of anthrax exposure. An expert review of published data on experiences with doxycycline use during pregnancy by TERIS - the Teratogen Information System - concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (the quantity and quality of data were assessed as limited to fair), but the data are insufficient to state that there is no risk.

A case-control study (18,515 mothers of infants with congenital anomalies and 32,804 mothers of infants with no congenital anomalies) shows a weak but marginally statistically significant association with total malformations and use of doxycycline anytime during pregnancy. (Sixty-three (0.19%)

of the controls and 56 (0.30%) of the cases were treated with doxycycline.) This association was not seen when the analysis was confined to maternal treatment during the period of organogenesis (i.e., in the second and third months of gestation) with the exception of a marginal relationship with neural tube defect based on only two exposed cases.²

A small prospective study of 81 pregnancies describes 43 pregnant women treated for 10 days with doxycycline during early first trimester. All mothers reported their exposed infants were normal at 1 year of age.³

Labor and Delivery: The effect of tetracyclines on labor and delivery is unknown.

Nursing Mothers: Tetracyclines are excreted in human milk, however, the extent of absorption of tetracyclines, including doxycycline, by the breastfed infant is not known. Short-term use by lactating women is not necessarily contraindicated; however, the effects of prolonged exposure to doxycycline in breast milk are unknown.⁴ Because of the potential for adverse reactions in nursing infants from doxycycline, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. (See **WARNINGS**.)

Pediatric Use: See **WARNINGS** and **DOSAGE AND ADMINISTRATION** sections.

ADVERSE REACTIONS

Due to oral doxycycline's virtually complete absorption, side effects to the lower bowel, particularly diarrhea, have been infrequent. The following adverse reactions have been observed in patients receiving tetracyclines.

Gastrointestinal: Anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, and inflammatory lesions (with monilial overgrowth) in the anogenital region. These reactions have been caused by both the oral and parenteral administration of tetracyclines. Rare instances of esophagitis and esophageal ulcerations have been reported in patients receiving capsule and tablet forms of drugs in the tetracycline class. Most of these patients took medications immediately before going to bed. (See **DOSAGE AND ADMINISTRATION**.)

Skin: Maculopapular and erythematous rashes. Exfoliative dermatitis has been reported but is uncommon. Photosensitivity is discussed above. (See **WARNINGS**.)

Renal toxicity: Rise in BUN has been reported and is apparently dose related. (See **WARNINGS**.)

Hypersensitivity reactions: Urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, pericarditis, and exacerbation of systemic lupus erythematosus.

Blood: Hemolytic anemia, thrombocytopenia, neutropenia, and eosinophilia have been reported with tetracyclines.

Other: Bulging fontanels in infants and intracranial hypertension in adults. (See **PRECAUTIONS-General**.)

When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic discoloration of the thyroid gland. No abnormalities of thyroid function are known to occur.

OVERDOSAGE

In case of overdosage, discontinue medication, treat symptomatically and institute supportive measures. Dialysis does not alter serum half-life, and it would not be of benefit in treating cases of overdosage.

DOSAGE AND ADMINISTRATION

THE USUAL DOSAGE AND FREQUENCY OF ADMINISTRATION OF DOXYCYCLINE DIFFERS FROM THAT OF THE OTHER TETRACYCLINES. EXCEEDING THE RECOMMENDED DOSAGE MAY RESULT IN AN INCREASED INCIDENCE OF SIDE EFFECTS.

Adults: The usual dose of oral doxycycline is 200 mg on the first day of treatment (administered 100 mg every 12 hours or 50 mg every 6 hours) followed by a maintenance dose of 100 mg/day. The maintenance dose may be administered as a single dose or as 50 mg every 12 hours. In the management of more severe infections (particularly chronic infections of the urinary tract), 100 mg every 12 hours is recommended.

For pediatric patients above eight years of age: The recommended dosage schedule for pediatric patients weighing 100 pounds or less is 2 mg/lb of body weight divided into two doses on the first day of treatment, followed by 1 mg/lb of body weight given as a single daily dose or divided into two doses, on subsequent days. For more severe infections up to 2 mg/lb of body weight may be used. For pediatric patients over 100 pounds the usual adult dose should be used.

Administration of adequate amounts of fluid along with capsule and tablet forms of drugs in the tetracycline class is recommended to wash down the drugs and reduce the risk of esophageal irritation and ulceration. (See **ADVERSE REACTIONS**.) If gastric irritation occurs, doxycycline may be given with food. Ingestion of a high fat meal has been shown to delay the time to peak plasma concentrations by an average of one hour and 20 minutes. However, in the same study, food enhanced the average peak concentration by 7.5% and the area under the curve by 5.7%.

HOW SUPPLIED

Doxycycline Capsules 150 mg have a peach opaque cap printed "ADOXA[®]" in black ink/peach opaque body printed "150 mg" in black ink. Each capsule contains doxycycline monohydrate equivalent to 150 mg of doxycycline. They are supplied as follows:

Bottle of 60 NDC 10337-815-06

Store at controlled room temperature 15°-30°C (59°-86°F). (See USP).

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at the lesion sites. These are usually mild to moderate grade 1 or 2 side effects that resolve with corticosteroid therapy or discontinuation of the biologic agent.

Gastrointestinal IRAEs most often consist of mild to moderate enterocolitis. But occasionally, the colitis is grade 3, marked by bloody diarrhea, or grade 4, involving perforation, which is potentially fatal. Aggressive medical management, often including high doses of steroids, is sometimes required to control these toxicities.

Endocrinologic IRAEs are particularly puzzling, because they involve mainly the pituitary, a gland ordinarily very well protected against autoimmune disease. But a small number of patients with metastatic melanoma or renal cancer who are placed on anti-CTLA4 monoclonal antibody therapy—less than 1% thus far—develop autoimmune hypophysitis.

"You go into an Addisonian crisis. It's not a small thing. At the sella turcica, you see a swollen pituitary gland, which will become normal again after you've stopped therapy. You need to intervene here with corticosteroids and hormone substitution," he continued.

The most intriguing thing about the IRAEs is their strong correlation with induction of tumor regression. Investigators at the National Cancer Institute reported on 198 patients with metastatic melanoma or renal cell carcinoma treated with the CTLA4 monoclonal antibody ipilimumab. Twenty-one percent of the treated patients developed grade 3 or 4 autoimmune enterocolitis. The objective tumor response rate was 36% in those melanoma patients with colitis and 11% in those without. Similarly, 35% of renal cell carcinoma patients with colitis had an objective tumor response, compared with just 2% without colitis (*J. Clin. Oncol.* 2006;24:2283-9).

Dr. Eggermont is a consultant to Bristol-Myers Squibb Co., which together with Medarex Inc., is developing ipilimumab. The other CTLA4 blocker in clinical development is a Pfizer drug known for now as CP-675,206. ■