New Anticancer Agents Have Distinctive Toxicities

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AMSTERDAM — The highly promising new class of investigational anticancer agents known at 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 endocrinologic 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 regulator 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 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.

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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. ■

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