Ipilimumab Side Effects Not Quelled by GI Drug

BY NEIL OSTERWEIL
Contributing Writer

CHICAGO — The investigational agent ipilimumab showed activity against all stages of advanced metastatic melanoma, but was also associated with colitis and diarrhea that were not controlled by oral prophylaxis with the anti-inflammatory budesonide, investigators reported at the annual meeting of the American Society of Clinical Oncology.

"Ipilimumab, which in my opinion is an active drug in melanoma, is associated with autoinflammatory side effects, so-called immune-related adverse events," said Dr. Jeffrey S. Weber of the H. Lee Moffitt Cancer Center and Research Institute in Tampa, Fla.

The hypothesis of the study, funded by Bristol-Myers Squibb, joint developer of the monoclonal antibody ipilimumab, was that prophylactic oral budesonide (Entocort EC), an anti-inflammatory approved for treatment of Crohn's disease, might reduce the rate of grade 2 or greater gastrointestinal immune-related adverse events associated with ipilimumab therapy.

The idea did not pan out and the study did not reach its primary end point, although it did meet several of the secondary end points of melanoma control in both previously treated and treatment-naïve patients, reported Dr. Weber, who shares a patent with the University of Southern California and Bristol-Myers Squibb/Medarex.

Budesonide was chosen because it is a controlled-release oral steroid with minimal systemic corticosteroid exposure, Dr. Weber noted.

The primary end point of the study was diarrhea of grade 2 severity or greater among patients receiving 10 mg/kg of ipilimumab and either placebo or budesonide.

Secondary end points included best overall response rate per modified World Health Organization criteria, disease control rate (a composite of complete and partial response rates and stable disease), overall and 1-year survival, and biologic and pharmacokinetic parameters.

Budesonide was administered at a dose of 9 mg/day during ipilimumab induction every 3 weeks in four cycles over 12 weeks, after which budesonide was tapered. A total of 58 patients received the monoclonal antibody plus budesonide, and 57 received ipilimumab plus placebo.

The authors found that grade 2 or greater diarrhea occurred in 19 of the 58 (32.83%) of patients on budesonide, and 20 of 57 (35.1%) of those on placebo; the difference was not statistically significant, Dr. Weber said.

Objective tumor response to ipilimumab was seen in both the budesonide and control arms, at 15.8% and 12.1% of patients, respectively. Response rates were similar among previously treated and treatment-naïve patients, and in patients with stage M1a, M1b, and M1c disease. At the time of the analysis, 24 months, median overall survival had not been reached. The 1-year survival rate was similar in both groups, at 58.8% among patients on budesonide, and 59.1% of controls.

A Kaplan-Meier estimate for overall survival suggested that at about 20 months the survival rate for previously untreated patients would be 67.2%, and the rate for treatment-experienced patients would be 48.8%.

Among patients with melanoma metastatic to brain, two had a partial response, three had stable disease, one had disease progression, and one patient's status was unknown. Of these patients, one survived less than 6 months after being started on ipilimumab, four lived between 6 and 9 months, and seven were still alive from 10.4 to 19.4 months, the point of most recent follow-up.

Central nervous system adverse events related to ipilimumab were reported in two patients, with grade 2 headache and grade 1 dizziness. Immune-related adverse events were the most common toxicities seen with ipilimumab; 40% were grade 3 or 4 events. There were no bowel perforations or treatment-related deaths.

"My conclusion as to the secondary end points is that ipilimumab showed significant efficacy with an excellent estimated median overall survival in patients who got or did not receive prophylactic budesonide, previously treated or untreated patients, patients at all M stages, and including the 50% who had M1c disease," Dr. Weber said. ■

Nevi Do Not Develop Into Melanoma, Expert Suggests

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

WILLIAMSBURG, VA. — Although large numbers of nevi—especially dysplastic nevi—are clearly associated with an increased melanoma risk, the lesions themselves do not appear to become cancerous, Dr. Terry L. Barrett said at the annual meeting of the American Society for Mohs Surgery.

"I remain unconvinced that either the common acquired nevus or the dysplastic nevus develops into melanoma," said Dr. Barrett, professor of pathology and dermatology at the University of Texas, Dallas. "I think they are both benign lesions the majority of the time. Usually, melanomas in these patients arise on normal-appearing skin and not the site of the nevus. When that happens, I think it's coincidental, not a nevus gone bad."

Few studies have actually investigated this point, although Dr. Barrett did mention a 2007 in vitro study that looked at levels of polycomb group protein EZH2, a cell regulatory protein markedly elevated in malignant skin lesions (J. Cutan. Pathol. 2007;34:597-600). The level in both in situ and invasive melanoma was almost three times that seen in acquired and dysplastic nevi—a finding that seems to support Dr. Barrett's opinion.

Regardless of the source, however, patients with large numbers of nevi are at a significantly increased risk of melanoma and other malignancies. The two commonly recognized nevi syndromes carry different risks, Dr. Barrett said.

Familial atypical mole/melanoma syndrome is an autosomal dominant disorder that increases the lifetime risk of melanoma by almost 100%. Sporadic dysplastic nevus syndrome is a spontaneous mutation that increases the relative risk of malignancy up to 46 times that of the general population, he said.

For patients with the sporadic syndrome, sun exposure seems to play a key role in the development of melanoma. "It's been suggested that intermittent sun exposure manifests the phenotype of the dysplastic nevi [and its attendant increased melanoma risk], while patients without sun exposure manifest the common acquired nevi," Dr. Barrett noted.

"There is no clear agreement among dermatologists about how these lesions should be handled," he said. "If you think a lesion is premalignant, you'll want to excise it, and if the report comes back 'severely atypical,' you'll probably want to have negative margins. If you think the lesions aren't premalignant, then after you exclude a diagnosis of melanoma, you probably won't do anything. We have people in our practice who do both."

The phase in which a dermatologist "catches" the nevus probably influences treatment decisions. "These lesions are dynamic, change throughout life, and can be acquired at any age. I think what's happening is that if we biopsy them in a quiescent phase, we don't see cytological atypia. And if we catch them in a dynamic phase, they have different cellular characteristics, which we then have to define as mild or severe atypia," Dr. Barrett said.

Since the lesions are so changeable, and patients are at such a significantly increased risk of melanoma, close follow-up at 3- to 11-month intervals is crucial. It's probably a good idea to screen first-degree relatives, too, he suggested. ■

Dysplastic Nevi May be Linked To Neonatal Jaundice Therapy

BY BRUCE JANCIN
Denver Bureau

KYOTO, JAPAN — Blue-light phototherapy for neonatal jaundice could promote development of dysplastic nevi, Dr. Zsanett Csoma asserted at an international investigative dermatology meeting.

His latest contribution to the controversial issue was in the form of a study of 618 healthy Hungarian patients aged 21-71 years. Patients born since 1968—when blue-light phototherapy for neonatal jaundice was introduced in Hungary—were found to have a 2.1-fold greater prevalence of dysplastic nevi than those who were born earlier, Dr. Csoma said at a meeting of the European Society for Dermatological Research, the Japanese Society for Investigative Dermatology, and the Society for Investigative Dermatology.

In an earlier cross-sectional study involving 747 patients aged 14-18 years, he found the prevalence of clinically dysplastic nevi to be 19% in those with no history of phototherapy for neonatal jaundice, compared with 25% in patients with such a history.

The proposed mechanism for the increase in dysplastic nevi lies in the emission spectrum of blue-light photo lamps, according to Dr. Csoma of the University of Szeged (Hungary). Although the spectrum centers on 450 nm, a small proportion of the emitted light—less than 1%—is UVA. Ultraviolet light not only induces melanocyte proliferation, it also has profound immunosuppressive and immunomodulatory effects in the skin and is sufficient to induce melanoma precursors in animals. These immunosuppressive effects could be magnified in the immature skin of neonates, he said.

When the earlier study was published (Pediatrics 2007;119:1036-7), it drew fire from Dr. Phyllis A. Dennery and Dr. Scott Lorch of the University of Pennsylvania, Philadelphia, and Children's Hospital of Philadelphia, who wrote that they found the data unconvincing (Pediatrics 2007;120:247-8).

"We need to remember the devastating consequences of our reduced vigilance for hyperbilirubinemia in the late 1980s and early 1990s. We must seriously weigh the resurgence of kernicterus against the potential for moles and nevi until more strategies are available to prevent hyperbilirubinemia," they cautioned.

Separately, French investigators reported that neonatal phototherapy was associated with a significant increase in melanocytic nevi 2-5 mm in diameter in a study involving 58 children aged 8-9 years. They suggested melanoma surveillance in exposed children (Arch. Dermatol. 2006;142:1599-604).

The French recommendation was deemed "premature" in a follow-up commentary by Dr. Thomas B. Newman of the University of California, San Francisco, and Dr. M. Jeffrey Maisels, chairman of the department of pediatrics at William Beaumont Hospital, Royal Oak, Mich.

"Counseling families of infants exposed to phototherapy that their child needs to be watched for melanoma is not a trivial matter. Much more evidence than was provided … is needed before it can be recommended," they wrote (Arch. Dermatol. 2007;143:1216).

Dr. Csoma's study was supported by the National Fund of the Hungarian Ministry of Health. ■