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 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 grade of 2 or greater gastrointestinal immune-related adverse events associated with ipilimumab treatment.

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 metastatic melanoma patients and melanoma-naive 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 and progression-free survival (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 toal 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 (32.8%) 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 responses were 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-naive patients, in patients with both 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 treat ment—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 diziness. 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,” said the principal investigator, “but the excellent estimated median overall survival in patients who got or did not receive prophylactic budesonide, previ ously 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 risk of melanoma, 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—regardless of age—even though they change during the phases in which a dermatologist thinks a lesion is premalignant, you’ll want to ex clude a diagnosis of melanoma, you probably won’t do anything. We have people in our practice who do both.’

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 nevus syndromes carry different risk factors, 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 melanoma 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 nevus (and its attendant increased melanoma risk), while patients without sun exposure manifest the common acquired nevus,’ 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 exclude 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.’

Regardless of 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 characters—thus 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, Dr. Barrett said, ‘I personally like to biopsy them in a quiescent phase, and I don’t want to miss a malignant lesion.’

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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. Zsaznat Csoma asserted at an international investigative dermatology meeting.**

His latest contribution to the contro versial 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 jaund ice 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 in crease 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 effects. This can be observed on normal skin and is sufficient to induce melanocyte 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. Denny and Dr. Scott Lorich 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 re ported 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 surve illance in exposed children (Arch. Dermatol. 2006;142:1599-604).

The French recommendation was deemed “premature” in a follow-up com mentary by Dr. Thomas B. Newman of the University of California, San Francis co, 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 recom mended,” they wrote (Arch. Derma tol. 2007;141:1247-8).

Dr. Csoma’s study was supported by the National Fund of the Hungarian Min istry of Health.