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CAUSES OF CHILDHOOD CANCER NEWSLETTER

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For whom the Elidel tolls

Tacrolimus and pimecrolimus suppress T-cell response by inhibiting calcineurin, part of the signal transduction pathway that produces interleukin-2. When administered systemically in preparation for transplant, these drugs can lead to post-transplant lymphoproliferative disease (PTLD). Topical tacrolimus and pimecrolimus creams are eczema treatments marketed in the United States under the brand names Protopic and Elidel. These preparations appear neither to be absorbed systemically nor to interfere with T-cell function as measured by vaccine response. Nevertheless, the theoretical risk of cancer prompted the Food and Drug Administration (FDA) to require extensive postmarketing surveillance of the products as a condition of approval. In March 2005, the FDA issued a "black box warning" about Protopic and Elidel based on widespread off-label use in children under 2 years of age and "...on information about animal studies, case reports in a small number of patients, and knowledge of how drugs in this class work." The FDA advised that these drugs be used as second-line agents, that use be avoided in children under 2 years of age, and that they be used for short periods of time. **A.D. Ormerod** recently reviewed the evidence and weighed in on the FDA's decision in an editorial [**Br J Dermatol 2005; 153: 701-705**].

The case reports included 18 cancers of varying types following Protopic use and 10 cases following Elidel use, with three and four cancers, respectively, occurring in children. Elidel, especially, has been prescribed to children; 520,000 out of the estimated 814,138 person-years of exposure to the drug have occurred in children under 10 years of age. Based on the systemic use of tacrolimus and pimecrolimus, lymphoma was the greatest concern. Ormerod compared the incidence of lymphoma in children exposed to Elidel to that in the United States Surveillance, Epidemiology, and End Result (SEER) cancer registry. One case was reported versus 1.8 expected in children <5 years of age. No cases were reported in children 5-9, 10-14, and 15-19 years of age versus 1.0, 0.7, and 0.5 expected, respectively. The rate of reported lymphoma among Protopic users of any age was 0.65 cases per 100,000 versus 22 cases expected. Additionally, the types of lymphoma reported differed histologically from those seen in PTLD.

COMMENT: Ormerod's recounting of the evidence concerning calcineurin inhibitors and cancer was nuanced and informative. Self-reported surveillance data are not a substitute for rigorous follow-up and, as the FDA noted in its warning, "It may take human studies of ten years or longer to determine if use of Elidel [and Protopic] is linked to cancer." On the other hand, available evidence do not support the idea that calcineurin inhibitors used topically enter the body in large amounts. Also, a number of cancers would be expected to occur in any large population and the incidence of reported lymphoma, at least, was not elevated among users of Protopic and Elidel. Thus, in many ways the criteria that epidemiologists use to assess causality have not been met, which is why the European Agency for the Evaluation of Medicinal Products (equivalent to the FDA) and the American Academy of Allergy, Asthma, and Immunology declined to support the warning. This episode illustrates the difficulty of regulatory decision making under conditions of uncertainty. Logan G. Spector

More matter, with less ART?

Assisted reproductive technology (ART) describes a range of procedures which have facilitated the birth of many thousands of children since 1978. It is well established that ART increases the probability of multiple pregnancies and, independent of multiples, lowers the average birth weight of offspring. Associations of ART with birth defects [**see C3 Vol. 15, No. 4**] and childhood cancer [**see C3 Vol. 14, No. 1**] are suspected but difficult to verify due to the rarity of the conditions. A meta-analysis combines published estimates of risk to overcome small numbers. **Raimondi et al.** [**Br J Cancer 2005; 93: 1053-1056**] recently conducted a meta-analysis of eleven cohort studies of ART and childhood cancer. In each study the observed number of cancer cases were compared to the number expected based on national rate data. A meta-analytic standardized incidence ratio (SIR) was obtained by summing the observed and expected cases from each study; an exact confidence interval was obtained using the Poisson distribution. There were 47 cancers observed, versus 38.21 expected, among the 38,815 subjects in the combined cohort. The SIR was 1.23 (95% confidence interval: 0.93-1.37). Adjusting for study and exclusion of

three studies with irregular study designs did not change results. Additionally there was no evidence of publication bias.

COMMENT: While this meta-analysis provides some evidence that there is not a large, generalized increase in risk of overall childhood cancer associated with ART, the literature it summarized has several critical limitations. The combined cohort is still small, given the rarity of childhood cancer, and likely not powered to detect modestly increased risk. The analysis neither distinguished between technologies, which might confer differing levels of risk, nor did it consider maternal use of ovarian-stimulating drugs, for which a suggestion of increased risk of hematopoietic malignancies has been noted [see C3 Vol. 15, No. 2]. Finally, due to the small size of the cohort, heterogeneous cases of cancer were lumped together. However, it is preferable to examine diagnoses separately since etiology likely varies by cancer. The plausibility that ART increases risk of childhood cancer is greatest for embryonal tumors, which have abnormal gene imprinting in common. ART, in turn, seems to disrupt normal imprinting in animals and has been linked to imprinting disorders such as Beckwith-Wiedemann syndrome in humans. New approaches and larger numbers of cases are needed to address the still-smoldering issue of ART and cancer. Logan G. Spector

Brain Tumors: A Head's Up!

Numerous studies have reported a positive association between birth weight and childhood leukemia. Now, other newborn body measurements are being evaluated for associations with childhood malignancy. In this report, **Samuelson SO et al [Lancet Oncol 2005; 7:39-42]** investigated potential associations between the incidence of childhood brain tumor and birth characteristics including birth weight, gestational age, and head circumference. Records were linked between the Norwegian medical birth registry (1978-1998) and the Norwegian cancer registry (1978-2002). Over 1 million records were analyzed with over 12 million person years of follow-up. A total of 453 individuals aged 0-15 years were diagnosed with brain cancer during the time period. The authors found a positive association between head circumference and risk of brain cancer in children. Using 35cm as the reference group, the relative risk (RR) for developing brain cancer was 3.15 (95%CI=1.85-5.43) for infants with a head circumference greater than 38cm (after adjusting for birth weight, sex, and gestational age). Overall, there was a statistically significant 27% increased risk of brain cancer for each 1cm gain in head circumference. This positive association also appeared to be mostly confined to children diagnosed at 10 years of age or less. There was no association between head circumference and either leukemia or 'other' cancers. Although less precise, evaluation of specific subtypes of brain cancer did not reveal any differences. Interestingly, when the authors examined associations with birth weight (following adjustment for head circumference, gestational age, and sex), they found a statistically significant decreased risk (RR=0.74, 95% CI=0.58-0.96) with each 1kg decrease in birth weight. This suggests that high birth weight is also a risk factor for brain cancer in this study, although head

circumference and birth weight were highly correlated ($r=0.71$). The important finding is that after adjustment for birth weight, the magnitude of the RR for head circumference increased, which suggests that head circumference may be an independent risk factor for brain cancer.

COMMENT: This is the first study to suggest an association between head circumference and childhood cancer. The authors have no obvious explanation. While large head circumference may be a surrogate marker for undiagnosed cancer at birth, they argue that this is unlikely since the risk is increased for children up to the age of 10 years. Their data were also not consistent for slower growing brain tumors at birth. They suggest that growth factors necessary for neurogenesis may play a role in brain cancer. This would be similar to the theories regarding associations between high birth weight and childhood leukemia. Perhaps having a higher volume of vulnerable cells increases one's risk of developing cancer. Because neonatal measures are not subject to recall bias (they are available in medical records), these types of analyses are worthwhile to explore, particularly since they seem to suggest growth patterns may be cancer specific. Julie A. Ross

Childhood Cancer Research Network: Update

The Children's Oncology Group will be launching the Childhood Cancer Research Network (CCRN) under protocol (COG-AADM06N1) shortly. This protocol will serve as the registration process for patients and their parents and will enable them to participate in COG-sponsored studies. The registry protocol consists of two parts: consent without permission for future contact: this includes selected personal identifiers but no permission for future contact; and consent including permission for future contact: this includes personal identifiers along with permission for possible future contact.

Results of Pilot Study: In 2001, funds were received from the National Cancer Institute to pilot the CCRN (as COG AADM01P1) at approximately 10% of randomly-selected COG institutions in North America. Twenty-three institutions were selected. By March 2002, all institutions had obtained IRB approval to enroll patients. As of Dec 2005, 1848 parents/patients among these institutions have been approached for this protocol. Importantly, 1764 (~ 96%) have agreed to both levels of consent (consent for personal identifiers and for possible future contact), while 61 (3%) have agreed to release of personal identifiers only. Only 23 (1%) have refused both consent levels. The pilot of the CCRN is considered a major success. Moreover, many non-selected COG institutions have inquired about opening this protocol as a means to address HIPAA concerns and to facilitate enrollment on non-therapeutic research studies.

Given that COG treats the majority of children diagnosed with cancer in North America, the groupwide opening of the CCRN should enhance the conduct of non-therapeutic studies, such as epidemiology, biology, late effects, and cancer control. We will keep you updated. Julie A. Ross