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Study Solidifies Agent Orange and Myeloma Link

Exposure to the herbicide Agent Orange has long been considered a potential risk factor for multiple myeloma (MM) and its precursor condition, monoclonal gammopathy of undetermined significance (MGUS), although the science behind the association was limited.

Now, new research brings definitive evidence that Operation Ranch Hand veterans, U.S. Air Force (USAF) personnel who conducted aerial missions spraying the chemical during the Vietnam War, are more than two times as likely to have MGUS as other veterans (*JAMA Oncol* 2015;1[8]:1061-1068, PMID: 26335650).

“There has already been approval by the federal government to compensate people who served in the Vietnam War and developed lymphoma and myeloma, but there was no scientific evidence behind that—it was a political consensus,” said lead researcher C. Ola Landgren, MD, PhD a professor of medicine at Weill Cornell Medical College and the chief of the Myeloma Service at Memorial Sloan-Kettering Cancer Center, both in New York City. “That motivated my colleagues and me to follow up on prior findings and investigate the link between MGUS and exposure to Agent Orange.”

To do so, Dr. Landgren and his colleagues carried out a detailed examination of data and stored blood samples obtained from Operation Ranch Hand veterans and comparison veterans who served in Southeast Asia at the same time, from 1962 to 1971, but were not involved in herbicide spray missions.

The main goals of the study were to determine the prevalence of MGUS in Ranch Hand veterans compared with controls, and to assess the risk for MGUS related to the body burden of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), an Agent Orange component known to be a human carcinogen.

The study’s base population consisted of 1,951 USAF personnel who took part in the Air Force Health Study (AFHS), in which serum specimens were collected and stored at six intervals between 1982 and 2002. The investigators also had access to AFHS questionnaires and physical exam and laboratory data, which provided a wealth of information on age, race, military occupation, body mass index, smoking history, drinking history, history of cancer treatment and causes of death for deceased USAF personnel.

The final study population consisted of 479 Ranch Hand veterans and 479 controls, all men, with a median age of 65 years and with similar medical histories and demographic and lifestyle characteristics.

The researchers found the crude prevalence of MGUS to be 7.1% in Ranch Hand veterans and 3.1% in comparison veterans. Being a Ranch Hand veteran also correlated significantly with having increased body TCDD levels, with 47.5% of exposed veterans having levels above 10.92 parts per trillion (ppt) compared with 2.5% of the unexposed veterans. Furthermore, veterans with TCDD levels of 10.92 ppt or higher had a 2.43-fold greater prevalence of MGUS than those with 3.65 ppt or lower.

Dr. Landgren, whose previous research definitively linked MGUS to MM (*Blood* 2009;113[22]:5412-5417, PMID: 19179464), chose to look for MGUS because it is more common than MM; the AFHS, which used the disease and other rare cancers as end points, was underpowered to assess the effect of Agent Orange exposure on Ranch Hand veterans.

“If you want to study whether there is an association between a given exposure and the subsequent risk of developing a relatively rare cancer—such as multiple myeloma—unless you have a very large study population and/or a very long follow-up, statistically it becomes very imprecise, and you cannot reliably tell whether it is true or random. But if you use a more common surrogate end point—such as MGUS—then you have statistical power to study whether there is an increased risk or not,” Dr. Landgren explained.

“If there is a tight link to the precursor condition, that allows you to clearly study the exposure in relation to the cancer years ahead, because you have the information already from the precursor. The other option would be to follow people for 10 years and see what happens. That’s the rationale for studying the precursor in this setting,” he added.


Saad Usmani, MD

Saad Usmani, MD, the director of Plasma Cell Disorders at Levine Cancer Institute/Carolinas Healthcare System, in Charlotte, N.C., said the findings are provocative, although not surprising. “The association between Agent Orange and several malignancies, including hematologic malignancies, has been reported, but this is the most comprehensive study to show this to be true. This puts a number to the risk,” he said.

“It would be important to follow these patients prospectively and see what happens. Are they at high risk of developing active multiple myeloma, or even systemic amyloidosis? It is important to monitor those patients and see the natural history of this MGUS,” he noted.

At this point, there is no evidence that MGUS associated with Agent Orange exposure will behave differently from any other MGUS, said Dr. Landgren, who has found no difference in the risk for transformation across a wide variety of populations. “There is no data to suggest that the etiology leading from the precursor has a different trajectory.”

—*Monica J. Smith*

- See more at: http://www.clinicaloncology.com/ViewArticle.aspx?d=Hematologic+Malignancies&d_id=149&i=December+2015&i_id=1276&a_id=34555#sthash.ERPrHOEH.dCUS7NWt.dpuf
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