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Consensus Report of the 2015 Weinman International Conference on Mesothelioma

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Abstract

On November 9 and 10, 2015, the International Conference on Mesothelioma in Populations Exposed to Naturally Occurring Asbestiform Fibers was held at the University of Hawaii Cancer Center in Honolulu, Hawaii. The meeting was cosponsored by the International Association for the Study of Lung Cancer, and the agenda was designed with significant input from staff at the U.S. National Cancer Institute and National Institute of Environmental Health Sciences. A multidisciplinary group of participants presented updates reflecting a range of disciplinary perspectives, including mineralogy, geology, epidemiology, toxicology, biochemistry, molecular biology, genetics, public health, and clinical oncology. The group identified knowledge gaps that are barriers to preventing and treating malignant mesothelioma (MM) and the required next steps to address barriers. This manuscript reports the group's efforts and focus on strategies to limit risk to the population and reduce the incidence of MM. Four main topics were explored: genetic risk, environmental exposure, biomarkers, and clinical interventions. Genetics plays a critical role in MM when the disease occurs in carriers of germline BRCA1 associated protein 1 mutations. Moreover, it appears likely that, in addition to BRCA1 associated protein 1, other yet unknown genetic variants may also influence the individual risk for development of MM, especially after exposure to asbestos and related mineral fibers. MM is an almost entirely preventable malignancy as it is most often caused by exposure to commercial asbestos or mineral fibers with asbestos-like health effects, such as erionite. In the past in North America and in Europe, the most prominent source of exposure was related to occupation. Present regulations have reduced occupational exposure in these countries; however, some people continue to be exposed to previously installed asbestos in older construction and other settings. Moreover, an increasing number of people are being exposed in rural areas that contain noncommercial asbestos, erionite, and other mineral fibers in soil or rock (termed *naturally occurring asbestos* [NOA]) and are being developed. Public health authorities, scientists, residents, and other affected groups must work together in the areas where exposure to asbestos, including NOA, has been documented in the environment to mitigate or reduce this exposure. Although a blood biomarker validated to be effective for use in screening and identifying MM at an early stage in asbestos/ NOA-exposed populations is not currently available, novel biomarkers presented at the meeting, such as high mobility group box 1 and fibulin-3, are promising. There was general agreement that current treatment for MM, which is based on surgery and standard chemotherapy, has a modest effect on the overall survival (OS), which remains dismal. Additionally, although much needed novel therapeutic approaches for MM are being developed and explored in clinical trials, there is a critical need to invest in prevention research, in which there is a great opportunity to reduce the incidence and mortality from MM.

Keywords

Mesothelioma; BAP1; Asbestos; Erionite; Biomarkers; Genetics; Therapy

Introduction

The domestic and global burden of malignant mesothelioma (MM) remains substantial, with approximately 3200 cases per year in the United States[1] and 34,000 estimated deaths worldwide in 2013, respectively.[2] Despite encouraging advances in clarifying the underlying etiologic mechanisms, developing biomarkers for disease detection, and conducting novel clinical trials, the outlook for most patients in whom MM is diagnosed remains dismal. [3,4] Thus, presently the best strategy to reduce the terrible toll of MM is to prevent the disease from ever occurring (primary prevention).

The six types of minerals forming fibers that have been used commercially and fall under the umbrella term of *asbestos* include the serpentine mineral chrysotile and the fibrous amphiboles cummingtonite-grunerite (amosite asbestos), actinolite, anthophyllite, riebeckite (crocidolite asbestos), and tremolite.[5] Additionally, exposure to several other types of elongated mineral particles found in the natural environment and not specified in regulations as “asbestos,” such as fibers of the minerals erionite, winchite, richterite, antigorite, and fluoro-edenite, have also been associated with MM.[5]

The main preventable cause of MM has been exposure to commercial materials made or contaminated with asbestos.[6] Workplace exposure to commercial asbestos has affected occupational groups such as insulators and pipefitters, and their families with indirect “take-home” exposures transported by contaminated items such as clothing and contamination of the living environment from asbestos-containing products.[7] Starting in the 1980s when the mining and commercial use of these fibers was tightly regulated in some countries (e.g., the United States) and/or entirely prohibited in others (e.g., Western European countries), there was a drastic reduction in occupational exposure to asbestos.[8,9] However, asbestos continues to be used in Russia and many of the former Soviet republics, China, India, and many countries in the low- and medium-income range. Moreover, some of these countries have increased the use of asbestos exponentially in recent years, raising major concerns about a likely future increase in MM.[10]

An emerging problem is exposure of some populations residing in developing rural and desert areas to noncommercial asbestos and other types of mineral fibers present in the environment that have asbestos-like health effects.[5,11,12] The most notorious among these are fibers of the mineral erionite, a naturally occurring mineral fiber found in soil and rock that has been associated with very high rates of MM in Turkey.[12,13] Similarly, environmental exposure to the mineral fiber fluoroedenite, an amphibole species that occurs in the volcanic rock at the foot of the Etna volcano in Sicily, Italy, was linked to excess cases of MM among the villagers of Biancavilla in Sicily, Italy. Experimental evidence supports induction of peritoneal and pleural mesotheliomas induced by fluoro-edenite fibers present in Etnean volcanic material from Biancavilla.[14] Fibers of the mineral antigorite have been associated with an epidemic of MM in New Caledonia,[15] where it was found in the gravel used to pave

roads. These and other mineral fibers capable of causing MM are found throughout the United States, Europe, and many other parts of the world. When asbestos or other naturally occurring asbestos (NOA) are present in the environment, all age groups are exposed. A particular concern is when exposure begins in childhood, as this type of exposure may be associated with a greater risk for development of MM, because essentially all these individuals who reach adulthood will live long enough for MM to develop within the 30- to 60-year latency after exposure.

Recent studies have demonstrated that BRCA1 associated protein 1 (*BAP1*) germline mutations transmitted over the course of multiple generations are associated with a very high incidence of MM and other malignancies.[16–25] Multiple tumor types develop in family members who inherit BAP1 mutations; in addition, laboratory studies suggest that the incidence of MM may be increased upon exposure to asbestos, possibly even at levels too low to cause MM among the population at large.[26] Additional factors that have been associated in some studies with the development of some MM were not the focus of the meeting and are reviewed elsewhere.[27–29]

Methods

This meeting was organized to critically review and assess the strengths and weaknesses of new discoveries linking genetic risk and environmental exposure to the development of MM, the status of the current research, the possible use of MM biomarkers in prevention and early detection, and the benefit of novel molecularly based therapies versus standard clinical interventions. The goal of the meeting was to determine whether it would be possible to establish consensus among the participating experts on the current status of research in these areas and eventually propose specific actions/ guidelines to help further guide research and reduce the burden of mesothelioma.

The meeting organizers included the current chair (M.C.) and vice chair (S.K.) of the International Association for the Study of Lung Cancer Mesothelioma Task Force and the following National Institutes of Health staff: A.C. from the National Cancer Institute (NCI) Center for Global Health, S.M. from the NCI Clinical Investigations Branch, A.M. from the National Institute of Environmental Health Sciences, and A.W. from the NCI Center to Reduce Cancer Health Disparities. The meeting organizers invited the meeting participants, who are the coauthors of this manuscript. The need to have a multidisciplinary international team including some of the top experts in the field while keeping the number of participants within the available budget drove the criteria for selecting the meeting participants.

The meeting was held over a 2-day period and comprised six sessions that were chaired by the meeting organizers: Mineral Fiber Exposure and Rate of Disease Worldwide (chaired by M.C.), Mineralogy of Mesothelioma-Inducing Mineral Fibers (chaired by A.M.), Mineral Fiber Pathogenesis and Genetics (chaired by S.K.); Prevention and Early Detection (chaired by A.C.), Mineral Fiber Toxicology and Evidence of Adverse Health Effects from Exposure (chaired by A.W.) and State of the Art of Mesothelioma Treatment (chaired by S.M.). At the end of each session a 20-minute discussion was held. A 2-hour discussion/consensus-generating session was held on day 2 to review the current status of the field and the issues

presented. Each session chair wrote an initial draft summarizing the presentations and discussions of their respective session. After the meeting was completed, the organizers spent an additional day writing the first draft of the manuscript. This initial draft was circulated among all meeting participants multiple times until a final consensus manuscript was produced.

Genetic Risk

BAP1 is the first, and to date the only, gene that could increase the risk of cancer from asbestos and erionite exposure. Dr. Carbone and his team first discovered that the risk for development of MM was transmitted in an autosomal-dominant fashion in certain Turkish families in which MM developed in more than 50% of members.[13,30] In subsequent studies, the team found that germline mutations in the *BAP1* gene caused a novel cancer syndrome characterized by extremely high incidences of MM and uveal melanoma (UM)[16] and, less frequently, other cancers.[31] Moreover, characteristics of benign melanocytic skin lesions[32] that were initially considered part of the family of lesions known as atypical Spitz tumors often develop in these individuals. Subsequent analyses demonstrated that these lesions have unique histological and molecular characteristics setting them apart from atypical Spitz tumors, and they were named melanocytic BAP1-associated intradermal tumors (MBAITs),[31] a finding supported by subsequent studies.[33] The critical role of BAP1 in MM pathogenesis was further highlighted by the finding that BAP1 is the most frequently mutated gene in sporadic MM.[34–38]

BAP1 is a deubiquitylase that associates in the nucleus with multiprotein complexes regulating key cellular pathways, including the transcription, DNA replication, and DNA damage response pathways.[39–49] All germline *BAP1* mutations identified to date lead to inactive forms of BAP1 lacking deubiquitylating activity or to truncated variants that lack the nuclear localization signal.[50,51]

At least one malignancy has developed in all carriers of germline *BAP1* mutations who are older than 55 years studied so far, and multiple cancers have developed in many of them.[31] Familial MMs in these individuals occur in either the pleura or peritoneum (frequency ratio 1:1) at a median age of 56.3 years, have a male-to-female ratio of 0.73:1, and are associated with prolonged survival of 5 to10 or more years, compared with a median age at diagnosis of 72, a pleural-to-peritoneal ratio of 86:14, a male-to-female ratio of 4:1, and a median survival of less than 1 year in sporadic MM.[44] More than 50 families with this mutated BAP1 cancer syndrome have been described in the United States, Europe, and New Zealand.

In a large ongoing research effort to investigate the mutated BAP1 cancer syndrome, Carbone et al.[17] screened patients with family histories of multiple MMs and melanomas. They identified four families that shared an identical *BAP1* mutation and lived in different parts of the United States. After assessing family histories taken at the patient’s bedside, genealogy, and genetic analysis, they discovered a mutated BAP1 cancer syndrome kindred of approximately 80,000 descendants, whose family members descend from a couple born in Germany in 1710 (the man) and 1712 (the woman). The man’s ancestors were traced to Switzerland in 1588, and they immigrated to Germany in the 17th century. In the 18th

century, the couple immigrated to the United States and their descendants spread throughout the country, with carriers of the mutation affected by multiple malignancies.

These findings provide a guideline on how to integrate genomic and genealogical studies to identify additional branches of related families that may carry germline BAP1 mutations and benefit from genetic counseling and interventions for early detection and prevention.

Environmental Exposure

Environmental exposure to carcinogenic fibrous minerals includes indoor and outdoor contamination caused by both asbestos-containing commercial materials and NOA. The term *naturally occurring asbestos* is now widely used to describe potentially hazardous asbestos-like fibrous minerals that occur in rocks and soils, are often present in concentrations far lower than those necessary for mining, may or may not fit the regulatory or industrial definitions of asbestos, and may become airborne inhalation hazards after being aerosolized by human activity or natural surface processes.[52] Recent research suggests that NOA may be more common in our environment than previously thought.[5,53]

When conventional polarized light microscopy is used, the concentration of NOA in soils is often lower than the level of detection (<0.25%). However, when these soils with low concentrations of NOA are disturbed, potentially hazardous airborne exposures can be generated.[54,55] Accordingly, MM and other asbestos-related diseases have been documented from environmental exposure to NOA.[5] Documenting environmental exposures to NOA is much more challenging than is documenting occupational exposures.[5,11,12] Activity-based sampling measures concentrations of airborne fibers during typical human activities.[11,54] Because human activities are an important factor in disturbing and aerosolizing mineral fibers in the environment, activity-based sampling is extremely important to characterize and assess the health risks of environmental exposures. Assessing exposure to NOA requires testing for all potentially harmful fibrous minerals, not just those subject to government regulation.[11,53] Currently, most testing laboratories analyze only the regulated minerals, and therefore, they can often miss other mineral fibers that also have pathogenic importance.[56,57]

An alternative approach to investigating a high-risk exposed population for the purpose of documenting asbestos-like health effects is to screen people for benign pleural disease, which has a higher prevalence and shorter latency period than MM and can be detected by radiographic imaging.[58] Examples of this type of research include using plain chest radiography to screen the population of Libby, Montana, and chest computed tomography to evaluate potential health effects among workers in North Dakota who were exposed to erionite.[11,58]

Which dose metric best predicts disease risk is unclear. Although exposure to the six types of mineral fibers classified and regulated as “asbestos” has long been recognized as a causative factor in a spectrum of pulmonary and thoracic diseases, our understanding of the specific physiochemical risk factors associated with such adverse health effects has been limited by the analytical methods typically used to measure and describes exposures (i.e., using light microscopy techniques that count only a subpopulation of the actual airborne

fiber exposure and truncating analyses to only the six minerals typically regulated as "asbestos"). Use of higher-quality analytical technologies such as transmission electron microscope analyses[57] and better fiber counting rules would help us to better understand how fiber characteristics (e.g., chemistry, size, shape, surface area, etc.) are related to toxicity and risk of disease. Moreover, use of improved technologies and assessment approaches would greatly enhance our understanding of risk from exposure to other NOA-like mineral fibers, such as erionite, winchite, richterite, antigorite, fluoro-edenite, and other potentially carcinogenic mineral fibers that are not presently included in most analyses of exposure. Suboptimal and incomplete assessment of exposure interferes with our ability to assess the possible impact of NOA on risk for MM development of and other "asbestos"-related diseases. Several reviews and articles describe the proper methodology to detect both asbestos and NOA, and we refer to them for a detailed discussion.[52,56]

Research has been unable to clearly attribute adverse health effects to specific mineral fiber characteristics. Minerals known to be associated with MM are able to display a fibrous morphologic pattern, which is a direct result of their atomic structure. However, in nature, these minerals rarely occur as homogenous mineral deposits and exist as a continuum of particles of varying size, shape, crystalline structure, and chemical composition, which may or may not be further altered by natural environmental processes such as physical and chemical weathering.[56,59] This presents difficulty in understanding potential health risks attributable to specific natural mineral fibers. Determining cancer etiology is an intricate process because data from molecular biology, genetics, in vivo experiments, and epidemiology must be synthesized to gain a complete understanding of carcinogenicity.[60] Because of mixed and incomplete characterization of exposures in many studies, it has been difficult to relate specific adverse effects to specific sizes and types of fibers, etc. For example, the length and aspect ratio of fibers appear to be critical, with several studies demonstrating that greater toxic effects occur with longer fibers or greater aspect ratios. Longer fibers are retained for longer times in human lungs and thus exert their carcinogenic effect over the course of many years, whereas shorter fibers have a relatively more rapid turnover.[61] However, given a sufficient dose, fibers with a shorter or lower aspect ratio may still exert certain toxic effects, such as acute inflammation and fibrotic changes.[62] Experimental studies comparing lung function responses to NOA samples found that chrysotile was as fibrogenic as amphibole fibers and had detrimental effects on lung function[63] ; however, epidemiological studies indicate a lower risk for development of MM from exposure to chrysotile than from exposure to amphiboles.[6] In addition, studies of some other elongated mineral fibers, such as palygorskite, showed no substantive health effects.[64]

Studies regarding the mode of action of asbestos fibers indicate that mesothelial cells and macrophages, which are present in large numbers around asbestos deposits in the lung, produce a variety of deleterious mediators. These include high mobility group box 1 (HMGB1) and other cytokines, reactive oxygen species, and growth factors that promote sustained cell injury, inflammation, and DNA damage and stimulate cell growth, leading to fibrosis and/or carcinogenesis.[65–72]

Another approach to analyzing fiber exposure is to evaluate the mineral fiber content in the lung tissue of people with known exposure.[7,61,73] Some prior work has been done to assess

exposures from the natural environment by evaluating fiber content in sentinel animal species, such as wild rats.[74] One possible research strategy to assess the associations between fibers deposited in lung and MM, is to harvest lung tissue at the time of lung resections or at autopsy from patients with MM and from resident controls without MM. This type of study showed a lifetime mesothelioma risk of 0.02% per 1000 fibers per gram (amphibole fibers longer than 5 μm) in the United Kingdom, with no significant difference between amosite and crocidolite.[73] However, this type of research effort is fraught with challenges; for example, in the United States it has become increasingly difficult to obtain such samples, as autopsies are rare and medicolegal issues and lawyers often interfere with research efforts to obtain and study lung samples. Moreover, care must be taken in the interpretation of findings: all fibers, including asbestos and NOA, should be studied, and fiber populations retained in the lung may change over the long latency period between inhalation and development of MM. In this regard, it is generally accepted that some fibers such as chrysotile are digested by tissue macrophages and removed from the human lungs more quickly than are other fibers such as crocidolite and erionite, and that among these fibers, the longer the fiber, the longer they are retained in the lungs. It has been estimated that crocidolite has a half-life retention time in human lungs of 7 to 9 years[61,75] and that chrysotile is cleared faster, with a half-life retention in the lungs that was estimated from weeks or months[76] to 1 to 8 years, depending on the length of its fibers.[77]

Several epidemiological features are emerging that may indicate differences between patients with MM who had environmental exposure or genetic risk factors and patients with MM who are known to have had occupational exposure. MM caused by environmental exposure and/or reported in those with *BAP1* genetic mutations are more likely to be found in younger individuals and to have equal sex and pleural/peritoneal distributions. These clinical observations have been seen in the cases of MM occurring in Cappadocia, Turkey, and in New Caledonia, as well as among cases of MM occurring in families carrying *BAP1* germline mutations.[17,44]

In eastern China, the pattern of MM reported by Dr. Weimin Mao appears unique, with an unusual excess of peritoneal MM (pleural-to-peritoneal ratio of 1:2), female cases (male-to-female ratio of 1:2), and young age (<50 years). Direct occupational or occupationally related take-home exposures have been documented in only 12% of these cases. The cause in the remaining 88% of this series of Chinese patients is unclear, and studies to clarify whether issues such as environmental exposure to mineral fibers and possibly other agents, genetic risk factors, etc., underlie development of MM in this population are greatly needed. The Chinese findings are of exceptional interest, as they potentially point to a different set of events and etiologic factors that cause development of MM in predominantly young Asian women who have no occupational exposure to asbestos. Identifying the cause(s) of MM in these Chinese women is critical to developing specific preventive and therapeutic approaches to MM in this population. These studies may also help us understand the causes of MM (in particular, peritoneal MM) in young women with no apparent history of asbestos exposure, as an increasing number of such cases are also coming to our attention in the United States and Europe. For example, Lee et al. reported that of 64 patients (35 females and 29 males) with peritoneal MM, only five (8%) had a prior history of asbestos exposure. Of interest, 24 of 64 of these patients (38%) had had a prior abdominal operation, which was

identified as a risk factor in this study, suggesting the hypothesis that the inflammation related to the operation may have promoted the MM growth. Two patients had had radiation exposure and 31 had no known risk factors at all.[78]

Another lesson from the Chinese and European experiences is the need to carefully confirm diagnoses of MM by using state-of-the-art pathology techniques. An older study by Goldberg et al. reported that 33% of the diagnoses of MM in France could not be confirmed by an expert review panel.[79] At the conference, Dr. Pira et al. in Italy and Dr. Mao et al. in China reported a similar or higher percentage of erroneous diagnoses of MM that were often related to inadequate specimens: diagnoses based on cytologic examination or fine-needle aspiration rather than larger biopsy, diagnoses that were not supported by an adequate set of immunostains, or diagnoses made by pathologists or coroners (in the United States) who rarely see these malignancies. Therefore, in addition to precise assessment of exposure, accurate diagnosis of MM is greatly needed to ensure that cases of MM are not missed owing to erroneous diagnosis and to prevent misunderstanding of the etiology, clinical care, and potential for prevention by the inclusion of non-MM cases.

Biomarkers

Novel Potential Biomarkers of Asbestos Exposure and MM

HMGB1 is a damage-associated molecular pattern nuclear protein that is released by human mesothelial cells and macrophages undergoing programmed cell necrosis after exposure to asbestos fibers.[68] HMGB1 triggers the inflammatory response that over the years contributes to the development of MM.[80] Moreover, as MM grows out of an environment rich in HMGB1, MM cells are often “addicted” to HMGB1 and actively secrete HMGB1 in the extracellular space in which HMGB1 promotes MM tumor cell growth and invasion.[81] HMGB1 secretion requires its acetylation, which prevents the normal transport of HMGB1 from the cytoplasm to the nucleus. Patients who have documented exposure to asbestos have increased levels of HMGB1 in the serum[80–83]; levels of HMGB1 in asbestos workers were significantly higher than in individuals who were not exposed to asbestos or smokers with bronchial dysplasia and chronic inflammation. In asbestos-exposed individuals, most of the HMGB1 found in the serum is in the non-acetylated form, as is expected after passive release of HMGB1 on account of necrotic cell death induced by asbestos. The levels of HMGB1 are also increased in patients with MM patients to even higher levels than in asbestos workers, and most importantly, the serum of MM patients contains almost exclusively the hyper-acetylated form of HMGB1 and MM cells actively secrete HMGB1 to promote their own growth.[84] Presence of total and hyperacetylated HMGB1 was also sensitive and specific in identifying which patients with pleural effusions had a malignant effusion due to MM and which had benign or metastatic disease to the pleura. Among patients with malignant pleural effusions, sensitivity and specificity were increased when HMGB1 and fibulin-3 (see later) were measured together.

Additional potential novel biomarkers for MM include SOMAmers (SomaLogic, Inc., Boulder, CO), which are specifically designed short pieces of nucleic acids that bind selectively and specifically to individual proteins. Individual SOMAMer-predicted proteins have been validated using commercially available enzyme-linked immunosorbent assays,

and among them, the most promising is the SomaLogic 13 marker profile.[85] In a head-to-head comparison with soluble mesothelin– related protein (SMRP) with identical specimens, the SomaLogic profile had much greater sensitivity and specificity. Further validation studies using serum from cases with other malignancies compared with MM using a 13-marker panel is ongoing.

Biomarkers Studied for Early Detection and Diagnosis

Most of the biomarkers have been studied exclusively in pleural as opposed to peritoneal mesothelioma. After the groundbreaking work from Robinson et al. describing the use of SMRP for the diagnosis of MM in the Wittenoom Cohort of Western Australia,[86] the laboratories of Dr. Pass and Dr. Robinson performed a blinded SMRP validation of 817 asbestos-exposed individuals versus 168 people with MM (manuscript in preparation). This trial, with the SMRP measured blindly at two separate laboratories, validated in the area under the curve (AUC) of the receiver operating characteristic curve of 0.80 not only in the entire cohort but also in patients with stage I or II disease. Hollevoet et al. published an individual patient data meta-analysis of 1026 cases of MMs and 3465 controls based on data from 16 studies in the literature and further confirmed an AUC of 0.80.[87] An NCI Early Detection Research Network–sponsored assessment of the Vitamin C and Retinoic Acid study, in which 49 cases of MM were diagnosed in 3897 asbestos-exposed individuals who contributed sera for the chemoprevention study, revealed that the receiver operating characteristic of these 49 cases could generate an AUC of 0.72 at 1 year before the diagnosis when prediagnostic sera from these patients were used (manuscript in preparation). When the SMRP comparisons were performed any longer than 1 year before diagnosis, the ability to detect the disease was unsatisfactory. It was concluded that SMRP is a robust marker with good specificity, but its sensitivity (32% at 95%) has so far limited its application for early detection of MM in longitudinal follow-up of high-risk cohorts.[87]

Osteopontin (OPN) has also shown significant fold increases in MM compared with in controls, with ninefold increases documented ($p < 2 \times 10^{-13}$). Indeed, the original manuscript described remarkable AUCs close to 0.9 for serum OPN.[88] Unfortunately, it was learned that OPN is not specific for MM. Moreover, the inability of some laboratories to reproduce the results from the original paper was due to the fact that a thrombin cleavage molecule affected the levels of OPN measured when the measurement was performed in serum[89] and to the fact that OPN enzyme-linked immunosorbent assays differed in reliability. Subsequent investigators confirmed these findings by measuring OPN in plasma from malignant pleural mesotheliomas (MPMs) and control populations with a rise in the AUC to levels comparable to the rise in SMRP.[90–92]

Other markers, including fibronectin and thrombospondin, have been examined. The most promising seems to be a member of the fibulin family, fibulin 3 (FBLN3), the gene of which is EGF-containing fibulin-like extracellular matrix protein 1 gene (EFEMP1).[93] In the available literature, FBLN3 was found to be decreased in most tumors compared with normal tissue on account of methylation, whereas in MM, Pass et al. found that it was increased sevenfold ($p = 10^{-9}$) compared with normal mesothelium. Fibulin upregulation in MM was validated in silico by examining FBLN3 on expression arrays.[93] When MPM

cohorts from Detroit and New York were used, the AUC for FBLN3 compared with any controls was consistently greater than 0.95 and maintained 94% specificity at 100% sensitivity for stage I or II lung cancers. Levels of FBLN3 fell after successful cytoreduction and increased at the time of progression. A blinded validation from the Princess Margaret Cancer Centre in Canada maintained an AUC of 0.87. Moreover, pleural effusion FBLN3 was markedly increased and specific for MM effusions compared with benign effusions and effusions from other histological types of cancer. However, controversy persists regarding the role of FBLN3 in MM, with some reports validating the original publication[94] and failure to validate in others.[95–98] Validation of these early detection markers, as well as others involving microRNAs[99] in other study populations, is the next pressing issue.

Clinical Interventions

MM is heterogeneous in its clinical behavior according to sex, histological features, primary site of disease, and stage.[78,100–103] Although distant metastasis may occur,[3] most of the morbidity and mortality is due to local disease progression. Most of the available clinical information about treatment of early-stage MPM is derived from retrospective single-center series, and thus there is no consensus as to the optimal treatment.[104,105] The combination of pemetrexed and platinum is the only U.S. Food and Drug Administration (FDA)-approved regimen for patients with MPM who are either unresectable or otherwise not candidates for an operation. The recent French Mesothelioma Avastin Cisplatin Pemetrexed Study trial reported that the addition of bevacizumab to platinum-pemetrexed improved survival outcomes for patients with MM; however, this agent has not yet obtained FDA approval.

Although patients in whom MM was diagnosed and who were treated when it was in stage 1A experience survival of 3 or more years, in more than 95% of patients the diagnosis is made at a later stage, when median survival remains approximately 1 year from diagnosis.[3] The possible beneficial role of surgical resection in MPM remains controversial. The Mesothelioma and Radical Surgery trial from the United Kingdom provided the only randomized assessment of surgical management of MM and showed no additional survival benefit from an operation; actually, patients who had an operation did worse than those who were treated with only chemotherapy.[106,107] This trial was highly debated by experts in the field. The trial was not designed to answer the question of whether to perform an operation (only for the feasibility to randomize), and furthermore, the perioperative mortality rates were not acceptable and not representative. However, for selected patients with MM (those with early-stage disease, a good performance status, and epithelioid histologic findings and for whom the surgeon believes achieving a macroscopic cytoreduction [MCR] is possible), an operation is usually recommended.[108] The specific surgical procedure that accomplishes the MCR should be clearly defined according to the definitions of Rice et al.[109] There is no survival advantage to an R2 surgical resection that does not achieve complete macroscopic cytoreduction. Patients with MM who were selected for surgical resection as part of a trimodality treatment approach had median survival rates of 33.2 months if MCR (R0 or R1) was possible versus 12.9 months in patients for whom only an R2 resection was possible.[110] These survival differences reflect the impact of both the pathologic stage and extent of tumor at the time of surgery, as well as the importance of achieving complete local disease control. Therefore, if an R0 or R1 MCR cannot be achieved, local tumor control is not possible and

there is little survival benefit to the operation. In the absence of symptoms, these patients are better served with systemic therapies to treat all foci of disease and spared the morbidity of a major surgical resection. The role of an operation in MM for the purposes of symptom palliation for indications of persistently trapped lung or debulking of macroscopic disease remains pivotal.[111] Extrapleural pneumonectomy (EPP) with en bloc resection of the lung with the parietal and visceral pleural, pericardium, and diaphragm or lung-sparing pleurectomy/decortication (P/D), in which all macroscopic tumor on the parietal and visceral pleura is removed, are the two surgical procedures typically performed; these aggressive procedures should be performed by surgeons and in centers with appropriate expertise in these procedures.[3,112] There are no randomized trials that compare EPP with P/D, but retrospective analyses suggest that survival outcomes are similar and the choice of a specific procedure—EPP or P/D—is usually dictated by the surgeon's expertise.[3] Many things factor into the decision for EPP rather than P/D, including patient functional status, patients' desires after counseling, and which operation fits the preoperative or postoperative adjuvant protocols prescribed. A retrospective review of 663 patients who underwent an operation at three MM centers in the United States compared EPP with P/D and found that patients who underwent P/D had better survival than those who underwent EPP and that perioperative morbidity and mortality was greater after EPP.[3] The morbidity and mortality conclusions from this study have been validated by analyzing data from the Society of Thoracic Surgeons database.[112]

In patients with resectable MM, a trimodality approach is often used with radiation therapy to enhance local disease control and chemotherapy (systemic, either preoperative or postoperative, or intraoperative) to reduce the risk of local recurrence and systemic metastases. Although an OS advantage has not been demonstrated with these combined approaches in a randomized trial, this trimodality approach has been associated with relatively prolonged survival compared with chemotherapy alone as historical controls.[113–118] Nevertheless, a recent randomized trial has questioned the benefit of postoperative radiation therapy after extrapleural pneumonectomy[119]

In the United States, it is standard practice to administer four cycles of cisplatin-pemetrexed to multimodality therapy for resectable mesothelioma (National Comprehensive Cancer Network guidelines). Ultimately, the decision to administer neoadjuvant or adjuvant systemic therapy should be made in a multi-disciplinary setting. Neoadjuvant therapy has the inherent risk of adversely delaying the operation or causing complications, with the EPP completion rates ranging between 42% and 84%.[116,118,120–125] On the other hand, neoadjuvant therapy yields response rates between 29% and 44%[116,118] and can give prognostic information, with responders having better survival outcomes.[116] Adjuvant chemotherapy does not compromise surgical resection, but poor patient tolerance after an operation and radiation often preclude delivery of chemotherapy. To date, there have been no randomized trials comparing neoadjuvant or adjuvant therapy, and both approaches are accepted as standard practice.

Although trimodality therapy is standard practice, both neoadjuvant and adjuvant studies still yield median OS rates between only 16.6 and 25.5 months.[116,118,120,121,123,125–127] There is a clear need for the addition of novel agents or immunotherapies to trimodality

treatment to improve survival outcomes. These agents must improve response rates, have reasonably low toxicity profiles with no compromise of trimodality treatment, and be able to be administered in a maintenance setting. In addition, the trial designs should include tissue and radiographic correlates to facilitate development of predictive and prognostic biomarkers.

In the unresectable setting, the Mesothelioma Avastin Cisplatin Pemetrexed Study trial was discussed. This phase III trial was conducted by the Intergroupe Francophone de Cancerologie Thoracique; it randomized 448 chemonaive unresectable MPMs to platinum-pemetrexed (PC) n = 225) versus platinum-pemetrexed-bevacizumab (PCB) (n = 223).[128] The PC was given for six cycles in both arms and the bevacizumab was given for six cycles with chemotherapy and then continued as maintenance. PCB improved both progression-free survival (hazard risk = 0.61, $p < 0.0001$) and OS over PC (hazard risk = 0.77, $p = 0.0167$). The median OS was 18.8 months with PCB compared with 16.1 months for PC. The median progression-free survival was 9.2 months with PCB compared with 7.3 months with PC. This triplet regimen is in the process of undergoing evaluation by both European and U.S. regulatory agencies for approval. It would be the first novel agent approved for use in mesothelioma. In the frontline maintenance space, other agents have not succeeded. The Control of Mesothelioma with Maintenance Defactinib trial was a registration-directed phase II trial of maintenance therapy with a focal adhesion kinase inhibitor defactinib (VS-6063) in patients with MPM that unfortunately closed in September 2015 because of lack of efficacy.

A number of novel treatments for nonresectable MM that look promising at the exploratory stages are in clinical trials.[129] Mesothelin has been validated as an attractive target for cancer therapy. Several drugs targeting mesothelin, including immunotoxins (SS1P and RG7787),[130] a chimeric monoclonal antibody (amatuximab),[131] an antibody drug conjugate (anetumab ravtansine),[132] and a tumor vaccine (CRS-207), are in various stages of development to treat patients with mesothelin-expressing tumors, including MM. A phase II/III randomized clinical of amatuximab in combination with pemetrexed and cisplatin is currently open as frontline therapy for patients with pleural MM who are not candidates for an operation. Registration clinical trials of anetumab ravtansine and CRS-207,[133] a live attenuated *Listeria monocytogenes* engineered to express human mesothelin, are expected to open soon.

Checkpoint immunotherapies are also under investigation in unresectable mesothelioma. A mesothelioma cohort of KEYNOTE-028 (n = 25), which included only patients whose tumors were positive for PD-L1 expression and used pembrolizumab (a programmed cell death protein 1 inhibitor) reported a 24% overall response rate, 48% stable disease rate, and 76% disease control rate. This study is ongoing and accruing patients with unresectable mesothelioma.[134] However, immunotherapies require further investigation despite the initial promising results. A cytotoxic T-lymphocyte antigen-4 inhibitor, tremelimumab, was recently assessed in a randomized phase II trial (DETERMINE) in the salvage setting and was unfortunately a negative trial when compared with placebo (AstraZeneca press release).[135]

Patient advocacy efforts supported by the Mesothelioma Association Research Foundation have resulted in the introduction in the U.S. Congress of a bill to establish an MM patient registry. High-quality data from such a registry are essential in providing data to evaluate patient outcome, quality of life, and follow-up information; calculate survival rates; analyze referral patterns; allocate resources at the regional or state level; report cancer incidence; and identify unmet MM research needs.

The clinical session concluded with the consensus that because of the relative rarity of the disease, multi-disciplinary international efforts are needed to conduct and complete randomized clinical trials with clinically meaningful end points.

Findings and Actionable Guidelines to Reduce the Future Incidence of MM

The finding that BAP1 heterozygosity renders mice susceptible to low amounts of asbestos that rarely cause MM in wild-type mice supports the biologic plausibility for a similar activity in humans.[26] To date, none of the patients with MM who are germline carriers of *BAP1* mutations have had a history of occupational exposure to asbestos, indicating that MM can develop in these individuals with undetectable levels of exposure. However, on the basis of the study by Napolitano et al.[26] showing that MM developed in 30% of $BAP1^{+/-}$ mice when they were exposed to 0.5 mg of asbestos (an amount that rarely caused MM in wild-type control mice) and on the basis of a study by the team of J. R. Testa, as described by Xu et al.[136] showing that $BAP1^{+/-}$ mice exposed to 3 μg of asbestos have a higher incidence of MM than control mice, it is anticipated that carriers of germline *BAP1* mutations may be more sensitive than the population at large to low amounts of asbestos and NOA. It is therefore a reasonable precaution for germline carriers of the *BAP1* mutation to consider avoiding jobs associated with any possible asbestos exposure, including low levels of exposure, and avoiding residing in areas where asbestos and NOA are known to be present in the environment. Suggested guidelines for *BAP1* testing and monitoring of those found to have germline *BAP1* mutations are listed later in this article. Moreover, the presence of BAP1 mutations offers new potential therapeutic targets.[137] For example, BAP1 regulates the expression of histone deacetylases, and assessment of BAP1 may help identify patients who may be more likely to respond to histone deacetylase inhibitors.[138]

Further research is needed to understand the relative contribution of physiochemical characteristics (e.g., mineralogy, morphology, and surface area) to the toxicity of diverse natural mineral fibers.[139] Each of these attributes may influence fiber durability, deposition, and clearance and thus persistence in the body and subsequent development of disease. Inherent bioreactivity due to mineral fiber composition will further influence toxicity. Therefore, to ultimately understand the risks of exposure and prevent disease, it will be important to fully understand the concentrations and characteristics of the elongated mineral particles that are being inhaled by those at risk, carefully evaluate physiologic responses, and develop new dose-response metrics associated with earlier upstream bio-markers of exposure to reduce adverse health effects.

Intervention to reduce exposure has great potential to prevent development of MM and save lives. For example, even though much remains to be learned about environmental exposure

to noncommercial mineral fibers with asbestos-like health effects, examples exist in which sufficient evidence was developed to motivate public health action to protect exposed populations. When Cappadocia, Turkey, was faced with an outbreak in which MM developed in and caused the death of 50% of exposed people, the government intervened and, following the advice of scientists, built two new small villages to help eliminate environmental exposure of the population to erionite fibers.[12] In Libby, Montana, the Environmental Protection Agency took the unprecedented step of declaring a public health emergency and engaging in aggressive environmental cleanup during which contaminated surface soils were removed and replaced with clean fill (http://www2.epa.gov/region8/cleanup-activities-libby). Similar types of actions, albeit on a much smaller scale, have been performed around schools in El Dorado, California, and at Superfund sites across the United States. Off-road vehicle use, which produces air exposure to dust-containing carcinogenic mineral fibers, and public access have been restricted at Clear Creek, California.[54] The Calivaras Dam project in California rigorously monitors and controls worker exposure, as well as efforts to understand and reduce emissions that may affect the surrounding community (http://www.sfwater.org/modules/showdocument.aspx?documentid=4851). Fairfax County, Virginia, has publicly mapped areas of asbestos throughout the county and imposes various requirements for development and control of emissions (http://www.fairfaxcounty.gov/hd/chs/natural-asb.htm). In North Dakota, after the finding of widespread erionite contamination on more than 300 miles of gravel-containing erionite roads that led to air erionite concentrations in school buses similar to concentrations found in the MM villages in Cappadocia,[11] the state intervened to repave roads, schoolyards, etc., with erionite-free gravel. Moreover, the North Dakota Department of Health is working with counties and businesses to restrict use of erionite-containing gravel (https://www.ndhealth.gov/EHS/Erionite/).

In southern Nevada, after the finding of asbestos (mainly actinolite) and other NOA (erionite, winchite, richeterite, and magnesioriebekite) in the environment, especially in the area surrounding the city of Las Vegas,[59] and the parallel finding of an unusually high percentage of MM cases in young individuals living in the same area,[140] some initial steps are being taken to protect road construction workers from exposure caused by disturbing asbestos in place. Although these initial steps are encouraging, more should be done, including mapping precisely where the cases of MM in young individuals have occurred and studying the environment near their homes. It is also urgent to precisely map where mineral fibers with asbestos-like health effects are found, so that measures can be implemented to prevent human activities that disturb and aerosolize the fibers (such as off road-vehicle recreation, housing development, etc.) in those areas. Because fibers travel in the air, activities that disturb asbestos and NOA present in the environment lead to potentially high levels of exposure not only for those present in the area but potentially also for people living miles away, because mineral fibers may be carried by the wind for many miles.[59]

Ongoing exposure to asbestos and other hazardous mineral fibers in the environment underscores the need to base worker and community protections on an improved understanding of the specific physiochemical characteristics (i.e., morphology, surface area, and bio-persistence) and dose that make these fibers hazardous from the standpoints of both cancer and noncancer health effects. Therefore, geological areas of concern for exposure to

asbestos and NOA must be mapped and the associated exposures (i.e., activity-based exposures) measured. Once the presence of asbestos and related mineral fibers in the environment has been documented, a range of remediation and source control strategies can be implemented to help reduce exposures. Understanding that in some areas proximity to large deposits of asbestos and erionite exposure cannot be entirely eliminated, it is reasonable to predict that measures aimed at reducing exposure might save many lives in future generations that would otherwise be lost.

It is often argued that there are costs associated with preventive activities. From a humanitarian point of view, however, MM is a horrible way to die; thus, MM prevention is easily justifiable. From a purely economic point of view, these measures are also justifiable: it has been estimated that litigation costs the U.S. economy billions of dollars per year, and many large companies have gone into bankruptcy because of this litigation, resulting in tens of thousands of jobs lost.[141] Moreover, the costs associated with the treatment of patients with MM are upward of hundreds of thousand dollars per patient. It is easy to recognize that an investment toward reducing exposure to asbestos and NOA will result in significant economic return in the following decades— and most importantly, will save many lives.

More research is needed to address several practical questions and improve prevention. To start, among the approximately 400 mineral fibers present in nature, we need to identify those that have asbestos-like health effects and thus need to be included in exposure assessment and control. Also, we must conduct studies to establish at what level of exposure these mineral fibers can be considered acceptably safe. And we need to identify what are the most appropriate and effective strategies to reduce risk by controlling exposures.

In addition to preventing development of disease by preventing exposure, another approach to reduce the burden of MM is to improve disease outcome through early detection. In one study, HMGB1 produced an area under the curve (AUC) of 1.0 and a sensitivity and specificity of 100% to identify patients with MM. The potential impact of this research is significant because if the findings of Napolitano et al.[84] are independently validated, total HMGB1 could provide a useful blood biomarker to identify individuals who have been exposed to asbestos and are thus at risk for development of MM, and, among them, hyperacetylated HMGB1 could provide a blood biomarker to detect those in whom MM has developed. The role of these biomarkers for the prediagnosis of MM will, it is hoped, be addressed using the cohorts of the Prostate, Lung, Colon, and Ovarian Cancer Screening Trial in the near future. A clinical trial sponsored by the NCI Early Detection Research Network to validate HMGB1, as well as OPN, FBLN3, and SMRP, as biomarkers for the early detection of MM is planned for initiation in 2017.

Consensus Findings: Summary

Suggested Guidelines for BAP1 Genetic Screening

1. The group supported BAP1 screening of patients with MM occurring in the setting of a high-risk family history of MM, UM, cutaneous melanoma, renal cell carcinoma, cholangiocarcinoma, and basal cell carcinoma and/or a high family

incidence of multiple cancers and patients with MM carrying melanocytic *BAP1*-mutated atypical intradermal tumors known as MBAITs.

2. Because of economic concerns, the group was divided on the issue of screening for *BAP1* germline mutations in all sporadic cases of MM in the absence of MBAITS, UM, etc., or in the absence of a suggestive family history. Ideally, all patients with MM should be screened for *BAP1* germline mutations when the resources are available.

3. The group supported screening for *BAP1* germline mutations in families with high-risk features, such as three or more cases of any of the following cancers within two generations: MM, UM, renal cell carcinoma, and cholangiocarcinoma.

4. With regard to when to test, the group was supportive of “early”-age screening for *BAP1* germline mutations. The exact “early” age of testing for *BAP1* mutations was controversial. It was noted that the earliest melanoma detected in a *BAP1*-mutated germline carrier so far has been at the age of 19 years (this individual was cured by resection). In other cancer syndromes, such as the Lynch syndrome, it is generally advised to initiate screening 10 years before the earliest detected cancer. Thus, it was proposed that children may benefit from genetic testing, as those who are found to have inherited *BAP1* mutations may benefit from screening for melanoma.

5. In summary, the group was in support of medical screening for at-risk people who are carriers of *BAP1* germline mutations as follows: (1) annual dermatological screening for early detection of melanoma at age 18 or younger; (2) annual eye examination/ophthalmoscopy for UM at age 18 or younger; and (3) skin and eye examinations every 6 months after age of 30, when the frequency of cancer among carriers of germline *BAP1* mutations starts to increase.

6. Genetic counseling should be offered to all individuals tested for *BAP1.*

7. Those with *BAP1* germline mutations should be encouraged to participate in studies to improve early detection of MM (e.g., the planned biomarker studies). The group identified this population as a high-risk cohort in which early detection was greatly needed, and because of the high incidence of MM, the clinical effectiveness of novel MM therapies may be easier to demonstrate.

8. Insurance does not cover next-generation sequencing for MM. The group identified this issue as an important barrier to furthering the field and the availability of for MM is an unmet need that will require further research and funding support.

Mineral Fibers in the Environment

The group supported a range of activities as follows: (1) increase research to identify locations where potentially hazardous mineral fibers are found in the environment (specifically, a better understanding of the distribution of fibers in soils, and not just in the

bedrock, is needed); (2) evaluate the presence and extent of relevant environmental exposures in areas of concern by using activity-based sampling methods; (3) perform lung fiber content analyses on tissues obtained at autopsy or at time of surgery from residents of the area with or without MM to help in understanding exposure disease relationships; (4) improve characterization of fibers (size, shape, mineralogy, surface area, chemistry, etc.) and conduct research to better understand their specific effects on health (particularly in the setting of etiologic research, all potentially carcinogenic mineral fibers should be studied and reported when counting fibers to assess risk for development of MM and asbestos-associated disease, including mineral fibers shorter than 5 μm and with a diameter less than 0.25 μm, because presently only “asbestos fibers” are generally reported and as a result of this bias it is impossible to evaluate the overall contribution of other mineral fibers, such as NOA, to MM); (5) as another approach to documenting relevant environmental exposures to mineral fibers, perform studies using sentinel animals such as wild rats or other animal species to measure fibers in lungs in areas where environmental exposure is suspected; (6) increase understanding of human behaviors that cause fibers to become airborne, such as off-road vehicle recreation, housing development, and road construction, and use existing information and develop more comprehensive land management and behavior modification strategies to reduce human exposure to carcinogenic fibers; and (7) study unique situations of high risk for MM without apparent mineral fiber exposure, such as that reported in Eastern China.

Environmental Exposure and Mesothelioma

The group was in support of the idea that the epidemiological indicators of possible environmental exposure or genetic risk, or both, as the cause of MM in a defined population include the following: (1) a male-to-female ratio close to 1:1, (2) an excess of MM in individuals younger than 55 years at diagnosis; and (3) a pleural-to-peritoneal ratio close to 1:1.

When confronted with these findings (such as in Cappadocia, Libby, southern Nevada, New Caledonia, and most recently China), one should have a high index of suspicion that the causes of MM are either environmental, genetic, or a combination of both (i.e., gene-environment interaction, as observed in Cappadocia). Once the causes of MM have been identified, these cohorts are excellent candidates for interventions to prevent further exposures and for early disease detection to reduce MM in future generations and improve disease outcomes for at-risk individuals.

Biomarkers

The group unanimously supported continued efforts to identify and document effectiveness and validate biomarkers used for early detection of MM. In the case of HMGB1, validation studies are needed to verify that high levels of total HMGB1 can identify individuals exposed to asbestos and that among them, the hyperacetylated form of HMGB1 identifies those in whom MM has developed.

Clinical Interventions

The group unanimously agreed that additional research and support of clinical trials with novel agents and immunotherapies are greatly needed. Multidisciplinary randomized trials in the surgical setting with novel agents or immunotherapies combined with trimodality treatment should be supported, and resectable patients should be encouraged to participate in these trials. In the unresectable setting, as platinum-pemetrexed is the only FDA-approved regimen, patients should be directed to consider enrollment in novel therapeutic trials.

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