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Report From the Jerusalem Workshop on Lynch Syndrome-Hereditary Nonpolyposis Colorectal Cancer

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Abstract

A Workshop was held in Jerusalem, Israel, on October 26 and 27, 2009 to discuss the management of Lynch syndrome-hereditary nonpolyposis colorectal cancer (CRC), with the primary goal to develop consensus for the optimal management of this disease. A second goal was to identify areas of research with the potential to advance the clinical management of Lynch syndrome. The perspectives and recommendations from the workshop are meant to be a platform for discussion and deliberation. The Workshop was organized by Moshe Shike (Memorial Sloan Kettering Cancer Center, New York) and sponsored by The Colon Cancer Foundation. More details of each presentation are available in an on-line supplement.

Clinical Topics

Albert de la Chapelle (Ohio State University) discussed the population prevalence of Lynch syndrome and suggested screening strategies. A population-based study from Columbus, Ohio, estimated the prevalence of Lynch syndrome among all CRC patients to be 2.8%, and among all endometrial cancer patients to be 2.5%. Using these prevalence figures, the lifetime risks for CRC and endometrial cancer in the general population (6% and 4%, respectively) and the ~50% penetrance for the mismatch repair (MMR) gene mutations, one can estimate that the prevalence of Lynch syndrome in the general population is approximately 1 in 300. He recommended that all incident CRC tumors be screened for the disease using immunohistochemistry (IHC). Hans Vasen (Leiden University Medical Center, The Netherlands) reviewed the organ distribution of cancer risk in Lynch syndrome, and noted that cancers of the colon, rectum, endometrium, urinary collecting system, stomach, ovary, brain, and sebaceous glands (Muir-Torre syndrome) are definite members of Lynch syndrome tumor spectrum, whereas it is less certain that tumors of the pancreas, breast, and prostate are integral to this disease. He recommended colonoscopic screening every 1–2 years from an early age, and annually after age 40. Robert Kurtz (Memorial Sloan Kettering Cancer Center, New York) discussed the impact of upper gastrointestinal cancers in Lynch syndrome, and noted wide variations in the incidence of gastric cancer based on the geographical location of the registry. Zsofia Stadler (Memorial Sloan Kettering Cancer Center, New York) reviewed the incidence of nongastrointestinal cancers in the Lynch syndrome, and estimated that 2.3% of all endometrial cancers occur in Lynch syndrome

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Conflicts of interest
The authors disclose no conflicts.

patients. However, 20% of endometrial cancers have microsatellite instability (MSI) and most are due to non–Lynch syndrome inactivation of *MLH1*. The lifetime risk of ovarian cancer is 4%–12% in women with the Lynch syndrome, whereas the risk of urinary tract cancers is about 8%, with a substantially greater risk in *MSH2* families and in men. Deborah Schrag (Dana Farber Cancer Institute, Boston) noted that prognosis is significantly better with Lynch syndrome-associated tumors, as well as CRCs that have MSI unassociated with familial clustering. Jinru Shia (Memorial Sloan Kettering Cancer Center, New York) discussed the pathologic features of CRCs in the Lynch syndrome, including tumor-infiltrating lymphocytes, medullary tumors (which are quite specific for MSI tumors), stromal lymphocytes (which are made up of B-cells, and create the "Crohn's-like" reaction), and poor differentiation.

Genetics

Paivi Peltomaki (University of Helsinki, Finland) discussed the 4 genes involved in Lynch syndrome: *MSH2*, *MLH1*, *MSH6*, and *PMS2*. Each gene is prone to specific mutational alterations, and a useful database is the InSiGHT website (available: http://www.insight-group.org). Juul Wijnen (Leiden University Medical Center, The Netherlands) reviewed the technical complexities inherent in the genetic diagnosis of Lynch syndrome. To find all pathogenic mutations, one must use a comprehensive strategy testing for all types of genetic alterations, and integrate this information with IHC and MSI testing. With current technology for mutation analysis, approximately 30% of MMR mutations cannot be identified. Sapna Syngal (Dana Farber Cancer Institute and Brigham and Women's Hospital, Boston) discussed the PREMM1,2 model, an open-access, Internet-based program that utilizes personal and family history to provide an estimate that genetic testing for Lynch syndrome would find *MSH2* or *MLH1* mutations (available: http://www.dcfi.org/premm). Megan Hitchins (University of New South Wales, Australia) and Ajay Goel (Baylor University Medical Center, Dallas) discussed "constitutional epimutations" in the MMR genes. *MLH1* epimutations should be considered when there is a CRC with MSI and absent expression of *MLH1* and *PMS2* at IHC, and no genetic mutation in *MLH1*. The mechanisms responsible for constitutional epimutations are not known.

Diagnostic Challenges

Steven Gruber (University of Michigan School of Medicine, Ann Arbor) discussed the diagnostic challenge created by familial clusters of CRCs that are not Lynch syndrome. Approximately 40% of familial clusters of CRC meeting the Amsterdam criteria are not associated with a germline mutation in a DNA MMR gene, abnormal IHC, or MSI, and are therefore not Lynch syndrome. CRC is less highly penetrant in these families, occurs at older median ages, and the non-CRC tumors of the Lynch syndrome spectrum are not increased in these families. One name applied to this situation has been familial CRC type X. It was recommended that this term should be replaced. Antoni Castells (Barcelona, Spain) discussed strategies for the identification of Lynch syndrome cases. MSI testing is approximately equivalent to IHC for case finding. A Bayesian model to predict MMR mutation carriers was developed and compared with other computer-based predictive models. Yael Goldberg (Hadassah Medical Center, Hebrew University) discussed the identification of the Lynch syndrome in Israel, and the unique challenges presented by the distinct ethnic groups: Ashkenazi Jews, Sephardic Jews, and Arabs. Peter Propping (University of Bonn, Germany) discussed the German Hereditary Nonpolyposis Colorectal Cancer Consortium, which now has ~4500 families and 6000 individuals enrolled in the registry.

Basic Topics

Rick Fishel (Ohio State University, Columbus) discussed the biophysics of the interactions between the MMR proteins and DNA, the displacement of histone proteins by the MMR proteins, and described animal models under development to help identify effective preventive strategies. James Eshleman (The Johns Hopkins University, Baltimore) reviewed MSI, and noted that mutation rates at the HPRT locus are elevated 100-fold in the absence of DNA MMR activity. Mutation rates are higher at repetitive sequences (ie, microsatellites), and there is a 600-fold range of mutation rates between dinucleotide and hexanucleotide repeats, inversely proportional to the length of the repetitive element, but directly proportional to the number of repeated elements. C. Richard Boland (Baylor University Medical Center, Dallas) discussed the mutational target sequences of MSI that cause cancer, which should be distinguished from the common microsatellite mutations that are passengers. A group of ~41 genes encode mononucleotide repeats that run for ≥6 units, and these are common targets of mutation in MMR deficiency. William M. Grady (Fred Hutchison Cancer Research Center, Seattle) discussed “second hits” at DNA MMR genes in tumor DNA. Allelic loss owing to large or small chromosomal deletions, or mitotic recombination-mediated gene conversion may occur in CRCs with MSI, occurring in a range from 4% to 46% of tumors. Methylation of the promoter of the wild-type allele occurs in some cases, particularly at the *MLH1* locus, but less often at the *MSH2* locus as a somatic event. Somatic point mutations are thought to be the least common second-hit mechanism. Steven Gruber (University of Michigan School of Medicine, Ann Arbor) reviewed the growth pathways associated with MSI in the colon. He discussed the possibility that serrated adenomas may be the precursor lesion for sporadic MSI CRCs, but pointed out that it is uncertain whether this is relevant to the Lynch syndrome.

Tumor Immunology

Wolf Fridman and Jerome Galon (Cordeliers Research Center, Paris) discussed the local immune response to colorectal neoplasms. Tumor-infiltrating lymphocytes (TILs) are commonly seen in Lynch syndrome CRCs, and are associated with a better prognosis. Total lymphocyte counts in the tumors are not the best predictor of outcome; specific T-cell subsets indicate a protective response, whereas others predict a poor outcome. Possible therapeutic strategies based on the types of immune responses were discussed. It was suggested that a proper interpretation of the TIL response is more predictive of clinical outcome than traditional TNM staging.

Management

David Kelsen (Memorial Sloan Kettering Cancer Center, New York) noted that there have been mixed reports regarding the benefits of adjuvant chemotherapy for patients with MSI CRCs. Several studies have suggested no benefit or reduced survival. This topic was identified as one in particular need of additional research.

Prevention

John Burn (Newcastle University, Great Britain) discussed chemoprevention in Lynch syndrome. Their published randomized CAPP2 trial using 600 mg of aspirin and 30 g of resistant starch showed no benefit in reducing adenoma recurrence at 4 years. However, the post trial analysis of follow-up data up to 10 years after initiation of the study showed a significant reduction in the incidence of CRCs and endometrial cancers in the treated cohort. This suggests a provocative new preventive approach to the disease.

Recommendations of the 2009 Jerusalem Workshop

The following consensus recommendations were made by the members of the Jerusalem Workshop.

1. Clinical Recommendations

a. **Which CRC patients should be evaluated for Lynch syndrome?** A consensus recommendation was that all CRCs should be screened with IHC for the DNA MMR proteins. An additional suggestion was to consider Lynch syndrome in cases of endometrial and ovarian cancers. An initial suggestion was to screen tumors regardless of age, but the group gravitated towards screening CRCs in patients <70 years old, which would miss 13.6% of cases, but exclude nearly half of all CRCs from analysis. The final recommendation was that all CRC patients <70 years old should be tested using IHC for the 4 DNA MMR gene products, or alternatively, MSI. The dissenters did not want to exclude testing for those >70 years of age. A cost–benefit analysis is needed to determine the benefits and the costs of such a program. Some health care professionals consider IHC to be a genetic test that requires prior counseling and informed consent, but there was a strong consensus that MSI and IHC testing should not be considered genetic tests, and should be ordered by appropriate medical personnel as needed for medical care.

b. **What is the optimal approach to the medical management of patients with CRCs who have MSI?** This was an area of controversy; some felt that the evidence indicates that adjuvant chemotherapy is not appropriate for patients with stage II or III CRC with MSI. Others felt that the evidence was insufficient to reach this conclusion. The consensus recommendation was that more data from prospectively designed studies are needed to resolve this important question.

c. **Strategic approaches to case finding in Lynch syndrome.** Initial suspicion of Lynch syndrome may arise because of family history, abnormal IHC, or MSI. If abnormal IHC or MSI is present, all patients should be offered genetic counseling and undergo genetic testing for Lynch syndrome. If no tissue is available from any CRC patient, computerized analysis of the personal or family history should be used, and genetic testing performed based on the recommended cutoffs for that model. Although *BRAF* mutations are found in ~40%–80% of sporadic MSI CRCs, and not in Lynch syndrome, there was no consensus on its use. However, in CRCs with MSI and absent *MLH1* expression, analysis for *BRAF* mutation and/or methylation of the promoter of *MLH1* are recommended. BRAF analysis has no role in the evaluation of endometrial cancers. Constitutional methylation of *MLH1* should be considered when methylation is found in the CRC specimen, and there is a Lynch syndrome-like clinical presentation.

d. **Surveillance in the Lynch syndrome.** Annual colonoscopy was recommended for all patients who have a diagnosis of Lynch syndrome, because interval cancers occur when surveillance intervals of 2 or 3 years are used. Routine endoscopic screening for gastric cancer was not recommended, and urinary cytology has been shown to be insensitive and nonspecific, and not recommended for routine use.

e. **Optimize screening for extracolonic cancers, particularly endometrial, ovarian, urinary tract, and upper gastrointestinal cancers.** Screening for each of these cancers is suboptimal, and in need of development in Lynch syndrome patients.

2. Genetics, Biobanking, and Database Recommendations

a. **Dealing with minimal family histories.** Many Lynch syndrome families do not meet the Amsterdam criteria, and the Bethesda recommendations will not detect all CRCs with MSI. Moreover, many Lynch syndrome patients do not have sufficient family history data from which to construct adequate pedigrees. The consensus recommendation was to make greater use of the computerized models that predict the likelihood of making a definitive diagnosis of Lynch syndrome.

b. **Non-Lynch syndrome familial CRC.** Approximately 40% of families that meet the Amsterdam criteria do not have germline mutations in DNA MMR genes, and the CRCs do not have MSI. The cancer risks in these families are different from Lynch syndrome. Uniform nomenclature is required until specific groups are identified and linked to etiologic factors, which include, but are not limited to, genetic factors. Until the subgroups are identified, these familial clusters of non–Lynch syndrome CRC should simply be called “familial CRC.”

c. **Storage of paraffin tissues.** It was recommended that all hospital pathology departments store tumor specimens for an indefinite period of time.

3. Research Recommendations

a. **Use of adjuvant chemotherapy.** The use of adjuvant chemotherapy in Lynch syndrome remains controversial, and it is essential to determine whether this is helpful or harmful to such patients, including the utility of neoadjuvant therapy and the use of irinotecan as a specific agent against MSI CRCs.

b. **The unique immunologic issues of MSI CRCs.** A major initiative into the unique immunologic issues of MSI CRCs was recognized as a high priority. Analysis of T-cell subsets in TIL populations, their predictive values, and their impact on outcome and response to therapy were recommended. Can immunologic analyses predict the patients who should be treated, or the benefit from specific types of adjuvant chemotherapy? Is it possible to enhance the immune response against the cancers? Are there immune-sparing or immunostimulating regimens? Chemoprevention of Lynch syndrome is a high priority, and nutraceutical approaches should be pursued.

c. **IHC.** The use of by pathologists in community hospitals is strongly encouraged, and educational programs that facilitate a uniform and proper interpretation of IHC are recommended. Ideal screening regimens must be validated for early detection of urinary tract tumors, endometrial tumors, and ovarian tumors in Lynch syndrome.

d. **Causes.** The genetic (and other) causes of non-Lynch syndrome familial CRC should be determined.

e. **DNA MMR gene expression.** Basic studies should be undertaken to understand the regulation of DNA MMR gene expression, including studies of siRNAs, and the identification of new “druggable targets.”

f. **Mouse model.** The development of a clinically relevant mouse model of Lynch syndrome is needed.

g. **Therapeutic drugs.** The development of drugs that are specifically effective against DNA MMR-deficient cells is needed. Cell lines are currently available for Lynch syndrome-*MSH2*, -*MLH1*, and -*MSH6*; however, there is no in vitro model for defective *PMS2*.

h. **Clinical benefits.** A more complete analysis of the clinical benefit from partial and subtotal colectomies in Lynch syndrome patients is needed. How extended should the colectomies be to ensure optimal protection against metachronous cancer and still provide the best quality of life?

i. **Natural evolution.** We do not know enough about the natural evolution of Lynch syndrome neoplasms; it is widely assumed that these tumors grow more quickly than non–Lynch syndrome tumors.

j. **Reliability.** How reliable are IHC and MSI testing on colonoscopic biopsies?

k. **Impact.** The relative impact of Lynch syndrome in countries with low incidences of CRC should be a focus of collaborative studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Appendix

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