ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY

Abstract #312537

MMR deficiency can be overlooked in carriers of certain pathogenic variants by routine MSI and/or IHC testing in Lynch syndrome: Implications for a wider MMR deficiency testing.

Marija Staninova Stojovska, Katerina Kubelka Sabit, Dzengis Jasar, Rubens Jovanovic, Nadica Matevska, Biljana Angelovska, Nenad Mitrevski, Milco Panovski, Aleksandar J Dimovski; Center for Biomolecular Pharmaceutical Analyses, UKIM-Faculty of Pharmacy, Skopje, Macedonia, The former Yugoslav Republic of; Acibadem Sistina Hospital, Skopje, Macedonia, The former Yugoslav Republic of; Department of Pathology, UKIM-Faculty of Medicine, Skopje, Macedonia, The former Yugoslav Republic of; Institute of Radiotherapy and Oncology, Skopje, Macedonia; University Clinic for Radiotherapy and Oncology, UKIM - Faculty of Medicine, Skopje, Macedonia, The former Yugoslav Republic of; University Clinic for Abdominal Surgery, UKIM-Faculty of Medicine, Skopje, Macedonia, The former Yugoslav Republic of

Background: DNA mismatch repair (MMR) deficiency occurs in both inherited/sporadic colorectal cancer (CRC) and endometrial cancer, but it may also be found in some other types of cancer. At present, MMR status testing in clinical practice is recommended for all CRC patients in order to identify those who should be offered genetic testing for the Lynch syndrome (LS), inform disease prognosis, and guide therapeutic management.There are two commonly accepted methods for MMR deficiency analysis, one based on the detection of microsatellite instability (MSI) by PCR and the other based on the detection of protein expression of the MMR genes using immunohistochemistry (IHC). The objective of this study was to evaluate the concordance between IHC and MSI in tumors from 18 LS patients with known pathogenic germline variants in MMR genes (MLH1, MSH2, PMS2 and MSH6).

Methods: The MSI testing was performed using the five gene Bethesda panel (BAT25, BAT26, D2S123, D5S346, D17S250) while the IHC testing was done with the use of a standard 4 antibody panel (MLH1, MSH2, PMS2 and MSH6).

Results: High concordance of the two methods was observed in 13/18 (72.2%) patients, mainly with disruptive mutations in the MLH1, MSH2 and PMS2 genes. Inconsistent results were obtained in 5/18 (28.8%) patients, of whom two had a positive result only with the use of the PCR method [carriers of MLH1 c.62C > T (p.Ala21Val) and c.244A > G (p.Thr82Ala) missense variants], other two had a positive result only with IHC [carriers of MSH6 c.3514dupA (p.Arg1172LysfsTer5) and c.2384T > C (p.Ile795Thr)] and one patient had normal results using both methods (carrier of MSH6 c.457+1G > T splice site mutation that results in exon 3 skipping). A positive predictive value of either MSI or IHC used as a single methods for screening was 83.3%, which indicates that a substantial number of cases with MMR tumors can be misdiagnosed by using only either one or the other of these two methods.

Conclusions: These results have a potential implication not only for LS screening in CRC patients, but also for the detection of the MMR deficiency in patients with various tumors that might benefit from the checkpoint inhibitor

immunotherapy. The use of extended MSI NGS panels might provide a higher sensitivity for the detection of MMR deficiency compared to the standard MSI or ICH testing.

Title:
MMR deficiency can be overlooked in carriers of certain pathogenic variants by routine MSI and/or IHC testing in Lynch syndrome: Implications for a wider MMR deficiency testing.

Submitter's E-mail Address:
adimovski@ff.ukim.edu.mk

Is this a late-breaking data submission?
No

Is this abstract a clinical trial?
No

Research Funding Source:
Other -

Research Funding Source Name:
ICGEB, Trieste, Italy; Macedonian Academy of Sciences and Arts, Skopje, RN Macedonia

Are there additional sources of funding for your study?
No

Are patients still being accrued to the trial reported in this abstract?
No

Would like to be considered for a Merit Award:
No

Have the data in this abstract been presented at another major medical meeting?
No

Has this research been submitted for publication in a medical journal?
No

Type of Research:
Diagnostic Test/Assay

Research Category:
N/A

Continued Trial Accrual:

No

Received Grant funding:
No

Sponsor:
Aleksandar Dimovski

First Author

Presenting Author

Marija Staninova Stojovska, PhD
Center for Biomolecular Pharmaceutical Analyses, UKIM-Faculty of Pharmacy
Majka Tereza 47
Skopje,
Macedonia, The former Yugoslav Republic of
Email: marija.staninova@gmail.com

Click to view Conflict of Interest Disclosure

Second Author

Katerina Kubelka Sabit, MD, PhD
Acibadem Sistina Hospital
Skupi 5a
Skopje,
Macedonia, The former Yugoslav Republic of
Email: katerina.kubelka@acibademsistina.mk

Click to view Conflict of Interest Disclosure

Third Author

Dzengis Jasar, MD, PhD
Acibadem Sistina Hospital
Skupi 5a
Skopje,
Macedonia, The former Yugoslav Republic of
Email: dzengis.jasar@acibademsistina.mk

Click to view Conflict of Interest Disclosure

Fourth Author

Rubens Jovanovic, MD, PhD
Department of Pathology, UKIM-Faculty of Medicine
Majka Tereza 47
Skopje,
Macedonia, The former Yugoslav Republic of
Email: rubens973@yahoo.com

Click to view Conflict of Interest Disclosure

Fifth Author

Nadica Matevska, PhD
Center for Biomolecular Pharmaceutical Analyses, UKIM-Faculty of Pharmacy
Majka Tereza 47
Skopje,
Macedonia, The former Yugoslav Republic of
Email: nmatevska@ff.ukim.edu.mk

Click to view Conflict of Interest Disclosure

Sixth Author

Biljana Angelovska, MD
Institute of Radiotherapy and Oncology
Vodnjanska 17
Skopje,
Macedonia
Phone Number: +38923119694
Email: angelovskab@hotmail.com

Click to view Conflict of Interest Disclosure

Seventh Author

Nenad Mitrevski, MD
University Clinic for Radiotherapy and Oncology, UKIM - Faculty of Medicine
Majka Tereza 47
Skopje,
Macedonia, The former Yugoslav Republic of
Email: kate.janeska@manu.edu.mk

Click to view Conflict of Interest Disclosure

Eighth Author

Milco Panovski, MD
University Clinic for Abdominal Surgery, UKIM-Faculty of Medicine
Skopje,
Macedonia, The former Yugoslav Republic of
Email: milco@drpanovski.com.mk

Click to view Conflict of Interest Disclosure

Ninth Author

Corresponding Author

Aleksandar J Dimovski, MD, PhD
Center for Biomolecular Pharmaceutical Analyses, UKIM-Faculty of Pharmacy
Vodnjanska 47
Skopje,
Macedonia, The former Yugoslav Republic of

Phone Number: +38970355078
Email: a.dimovski@manu.edu.mk

Click to view Conflict of Interest Disclosure