European Review for Medical and Pharmacological Sciences 2020; 24: 481-482

Letter to the Editor

Current predictive pathology in the clinical setting of colorectal cancer

Dear Editor,

Colorectal adenocarcinoma (CRC) is the second most common cancer in women and the third most common cancer in men, affecting mainly people older than 65 years[1]. The highest incidence is observed in industrialized countries, but in the other countries the incidence is increasing. Consumption of alcohol, processed and red meat, and obesity, are demonstrated risk factors. Also, genetic predisposition plays a role, and some mutations are recognized risk factors. Furthermore, some genetic tumor syndromes were identified[2].

The efforts to find new targets brought to identify some predictive factors in CRC[3]. Two genes belong to MAPK pathway, RAS and B-RAF, HER2 is a transmembrane receptor implied in PI3K pathway, and microsatellites are four proteins which forming two heterodimers are designate to correct DNA errors. A recent study on VEGF-A and MMP-7 genes expression could assume a role in the next future if it will be confirmed their predictive role, but further studies are necessary[4].

RAS belongs to MAPK pathway, regulating cell proliferation. RAS gene mutations are the most prevalent in CRCs, particularly mutations of K-RAS (Kirsten rat sarcoma viral oncogene homolog), followed by N-RAS and, only occasionally, H-RAS mutations.

RAF is part of MAPK signaling pathway; therefore, its activation leads to uncontrolled cellular proliferation and growth. B-RAF mutation occurs in codon 600, almost always V600E and seldom V600K, and is less frequent than RAS mutation in CRCs.

In 2017 it was established by a joint consensus of the American Society for Clinical Pathology, College of American Pathologists, Association for molecular Pathology, and American Society of Clinical Oncology to test these mutations in order to choose the proper therapy[5]. It is already proven that RAS mutations are predictive of resistance to anti-EGFR therapy in metastatic colorectal cancer, while testing B-RAF is recommended for prognostic stratification. In fact, patients with B-RAF V600E mutation are requested to take anti-EGFR antibodies therapy in combination with other pathway inhibitors[6,7].

HER2/neu (or erbB-2), human epidermal growth factor receptor[2], is a transmembrane tyrosine kinase receptor, located on chromosome 17. The dimerization of this receptor activates many signal pathways, including MAPK, PI3K/akt, STAT, regulating cell proliferation and survival. HER2 amplification has been demonstrated in many cancers, mainly in breast and gastrointestinal tract cancers. HER2 status is usually detected on formalin fixed or paraffin-embedded tissues, and has an approved scoring system for CRCs, that needs further confirmation with ISH or FISH[8,9]. The possibility to treat cancer with specific immunotherapy gives a therapeutic option, although the prognostic value of HER2 in CRCs is still debated.

Microsatellite instability is a condition caused by a DNA mismatch repair defect that leads to a genetic hypermutability status. DNA mismatch repair is constituted of numerous proteins, responsible of recognizing and correct errors in DNA, which occurred during replication and recombination. The inherited DNA mismatch repair defect is implied in some human syndromes, while its epigenetic silencing can be found in sporadic cancers. The cancers with MSI are characterized by a high number of mutations[10,11]. Microsatellite instability can be revealed

Corresponding Author: Renato Franco, MD, Ph.D; renato.franco@unicampania.it

by immunohistochemical technics, determining the expression of four proteins, MSH2, MLH1, MSH6 and PMS2, which are involved in Lynch syndrome. About 75% of the CRCs cases are sporadic[12], but MSI detection is fundamental for cancer classification. The prognostic value is uncertain, but MSI could be a target for new therapies. Furthermore, recent studies are focusing on different forms of MSI expressed in other tumors[13].

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Berretta M, Cappellani A, Fiorica F, Nasti G, Frustaci S, Fisichella R, Bearz A, Talamini R, Lleshi A, Tambaro R, Cocciolo A, Ristagno M, Bolognese A, Basile F, Meneguzzo N, Berretta S, Tirelli U. FOLFOX4 in the treatment of metastatic colorectal cancer in elderly patients: a prospective study. Arch Gerontol Geriatr 2011; 52: 89-93.
2) Arvelo F, Sojo F, Cotte C. Biology of colorectal cancer. Ecancermedicalscience 2015; 9: 9: 520.
3) Berretta M, Alessandrini L, De Divitiis C, Nasti G, Lleshi A, Di Francia R, Facchini G, Cavaliere C, Buonerba C, Canzonieri V. Serum and tissue markers in colorectal cancer: state of art. Crit Rev Oncol Hematol 2017; 111: 103-116.
4) Pezeshkian Z, Forouzesh F, Peyravian N, Yaghoob-Taleghani M, Asadzadeh-Aghdaei H, Zali MR, Nazemalhosseini-Mojarad E. Clinicopathological correlations of VEGF-A and MMP-7 genes expression in different types of colorectal adenoma polyps. World Cancer Res J 2017; 4: e978.
5) Sepulveda AR, Hamilton SR, Allegra CJ, Grody W, Cushman-Vokoun AM, Funkhouser WK, Kopetz SE, Lieu C, Lindor NM, Minsky BD, Monzon FA, Sargent DJ, Singh VM, Willis J, Clark J, Colasacco C, Rumble RB, Temple-Smolkin R, Ventura CB, Nowak JA. Molecular biomarkers for the evaluation of colorectal cancer: Guideline from The American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and the American Society of Clinical Oncology. J Clin Oncol 2017; 1: 35: 1453-1486.
6) Benson AB, Venook AP, Cederquist L, Chan E, Chen YJ, Cooper HS, Deming D, Engstrom PF, Enzinger PC, Fichera A, Grem JL, Grothey A, Hochster HS, Hoffe S, Hunt S, Kamel A, Kirilcuk N, Krishnamurthi S, Messersmith WA, Mulcahy MF, Murphy JD, Nurkin S, Saltz L, Sharma S, Shibata D, Skibber JM, Sofocleous CT, Stoffel EM, Stotsky-Himelfarb E, Willett CG, Wu CS, Gregory KM, Freedman-Cass D. Clinical practice guidelines in oncology. J Natl Compr Cancer Netw 2017; 15: 370-398.
7) Benson AB, Venook AP, Al-Hawary MM, Cederquist L, Chen YJ, Ciombor KK, Cohen S, Cooper HS, Deming D, Engstrom PF, Grem JL, Grothey A, Hochster HS, Hoffe S, Hunt S, Kamel A, Kirilcuk N, Krishnamurthi S, Messersmith WA, Meyerhardt J, Mulcahy MF, Murphy JD, Nurkin S, Saltz L, Sharma S, Shibata D, Skibber JM, Sofocleous CT, Stoffel EM, Stotsky-Himelfarb E, Willett CG, Wuthrick E, Freedman-Cass DA, Gregory KM, Gurski L. Rectal cancer, version 2.2018 clinical practice guidelines in Oncology. J Natl Compr Cancer Netw 2018; 16: 874-901.
8) Panarese I, Ronchi A, Toni G, Costanzo RMA, Casaretta G, Giannatiempo R, Sabetta R, Franco R, Marino FZ. HER2 exression in gastrointestinal tumor. A focus on diagnostic algorithm of HER2 status from gastric to intestinal cancer. World Cancer Res J 2019; 6: 1-7.
9) Seo AN, Kwak Y, Kim DW, Kang SB, Choe G, Kim WH, Lee HS. HER2 status in colorectal cancer: its clinical significance and the relationship between HER2 gene amplification and expression. PLoS One 2014; 9: e98528.
10) Nojadeh JN, Sharif SB, Sakhinia E. Microsatellite instability in colorectal cancer. EXCLI J 2018; 17: 159-168.
11) Boland CR, Goel A. Microsatellite instability in colorectal cancer. Gastroenterology 2010; 138: 2073-2087: e3.
12) Jasperson KW, Tuohy TM, Neklason DW, Burt RW. Hereditary and familial colon cancer. Gastroenterology 2010; 138:2044-2058.
13) Mohammadpour S, Goodarzi HR, Jafarinia M, Porhoseingholi MA. Elevated microsatellite alterations at selected tetra-nucleotide repeats (EMAST) testing in colorectal cancer using the cost-effective QIAXCEL advanced platform. World Cancer Res J 2019; 6: 1-6.

G. Toni[1], R. Franco[1], R. Di Francia[2]

[1]Department of Mental and Physical Health and Preventive Medicine, Università degli Studi della Campania "Luigi Vanvitelli", Naples, Italy
[2]GORI Gruppo Oncologico Ricercatori Italiani, Pordenone (PN), Italy