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The Importance of Personalized medicine in Colorectal Cancer: Review Article

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Abstract

Colorectal cancer (CRC) is the third most common type of cancer worldwide. It develops through a gradual accumulation of genetic and epigenetic changes, leading to the transformation of normal colonic mucosa into invasive cancer. Approximately 90% of colorectal cancer cases are sporadic without family history or genetic predisposition, while in less than 10% a causative genetic event has been identified. Since personalized medicine works on three subjects of determining disease indices in people, choosing the best therapeutic method and predicting disease relapse, it seems that regarding colorectal cancer, more researches are required in order to achieve favorable results. The recent advances in molecular biology and the genetic classification of CRC are essential to individualize these therapies and will be basic for improving the treatment in the next years. We are optimistic about the success of personalized medicine for this disease.

INTRODUCTION

Colorectal cancer (CRC) is the third most common type of cancer worldwide. In 2008, an estimated 1.23 million new cases of CRC were diagnosed. Approximately 60% of cases occur in developed countries, with the highest estimated rates in Australia/New Zealand and Western Europe and the lowest rates in Africa and south-central Asia. CRC is a heterogeneous disease caused by the interaction between genetic and environmental factors (1).

Moreover CRC develops through a gradual accumulation of genetic and epigenetic changes, leading to the transformation of normal colonic mucosa into invasive cancer. It typically affects older adults, though it can happen at any age (2). It usually begins as small, noncancerous (benign) clumps of cells called polyps that form on the inside of the colon. Over time some of these polyps can become cancers. In general, colon cancer begins when healthy cells in the colon develop changes (mutations) in their DNA (3). A cell's DNA contains a set of instructions that tell a cell what to do. Factors that may increase the risk of colon cancer include older age, African-American race, a personal history of colorectal cancer or polyps, inflammatory intestinal conditions, family history of colon cancer, diabetes, Obesity (4).

Advances in the treatment of metastatic (CRC) have led to an improvement in survival from 12 months with fluorouracil monotherapy to approximately 2 years (5). Despite these advances, CRC remains the fourth most common cause of cancer death worldwide and therefore more effective treatments are urgently needed. The incidence of CRC can benefit from different strategies depending on its stage: health promotion through health education campaigns (when the disease is not yet present), the implementation of screening programs (for detection of the disease in its early stages), and the development of nearly personalized treatments according to both patient characteristics (age, sex) and the cancer itself (gene expression) (6, 7).

Although cancer incidence and prevalence are increasing at an alarming rate, progress in treatment has been slow, and treatment benefits are measured in weeks to months. Following advancements in diagnostic science and early detection markers, a number of cancer types can be detected before pathological symptoms develop (8). Factors that should be consideredin personalized medicine of CRC include patient's characteristics and unique properties of tumors that may also provide information about the prognosis of the disease. Sources of high heterogeneity in CRC patients are genetic and epigenetic alterations

such as chromosomal instability (CIN), Microsatellite instability (MSI) and CpG island methylator phenotype (CIMP) (9). Biomarkers are characteristics that indicate a normal or pathogenic process or a response to a specific therapeutic intervention. they may have prognostic and/or predictive value. These markers are biochemical, epigenetic, genetic, imaging, metabolomic, and proteomic (10). The design of new genetic and epigenetic marker panels may provide maximum coverage in the diagnosis of colorectal neoplasia seems a reasonable strategy. In recent years, the use of DNA, RNA and protein markers in different biological samples has been explored as other strategies for CRC diagnosis. This information is of great significance because individual specific treatment regimens can be designed based on the presence and stage of cancer as concluded from profiles of markers discussed above (11, 12).

The goal of personalized medicine is to use the right drug at the right dose, with minimal or no toxicity, for the right patient at the right time. Modern personalized medicine is based on targeted therapy. In targeted therapy, it is essential that knowledge's about the altered pathway and the components leading to cancer are available. The aim of this review is to summarize progress made in different areas of personalized therapy for CRC and to discuss advances in the field (13).

Molecular biology of colorectal cancer

Approximately 90% of colorectal cancer cases are sporadic without family history or genetic predisposition, while in less than 10% a causative genetic event has been identified. In most of these cases, the causative genetic event has been identified (14). However, up to 25% of cases have a family history of CRC (familial CRC), but are not consistent with one of the known inherited syndromes. They have a higher risk of developing CRC in comparison with the general population, although not as high as in the inherited syndromes (15). Most of the CRC cases however are sporadic, in which there is no family history or genetic predisposition. Many efforts have been made on discovering the genomic changes in colon cancer and recently the Cancer genome atlas network published the somatic alterations in 276 colon cancer samples by analyzing the exome sequence, DNA copy number, promotor methylation, mRNA and microRNA expression (16). The most common genetic changes that have been found in sporadic CRC are activating mutations of the oncogene KRAS and silencing mutations of the tumor suppressor genes APC, SMAD4 and p53, along with multiple alleic losses (5q, 17q and 18q). Specific signaling pathways or genes have been found to be commonly affected in CRC. For example, almost 100% of tumours have changes in MYC transcriptional targets, 93% of in the WNT signaling pathway, 55% of tumours have alterations in KRAS, BRAF or NRAS and 33% in both the phosphoinositol 3 kinase (PI3K) and RAS pathways (7, 17).

Methylating pathway tumors occur more frequently in women and elderly people, are preferably located in the right colon and do not benefit from treatment with 5-fluorouracil (5-FU) (18). The tumors with BRAF mutation are histologically poorly differentiated with mucinous differentiation or signet rings, that exhibit microsatellite instability and the precursor lesions of these CIMP (CpG island methylator Phenotype) tumors are sessile serrated adenomas (19).

There is increasing interest in using genetic changes as biomarkers to help guide systemic therapy. Biomarkers are biological molecules found in the body that can be assessed (as present or absent) or measured (from low to high level) to indicate a particular disease. Prognostic biomarkers indicate overall survival, independent of what treatment is given. Predictive biomarkers indicate the likelihood of responding to a particular treatment. Below is a summary of the main genetic changes in colorectal cancer that may be used as prognostic and/or predictive biomarkers for treatment (20).

KRAS

The KRAS gene belongs to the RAS gene family involved in signaling pathways that regulate cellular proliferation, differentiation or survival. Oncogenic mutations in the RAS gene have been identified in ~30% of all human tumors, in which mutations in KRAS accounted for ~85%, NRAS proto-oncogene GTPase (NRAS) for ~15%, and HRas proto-oncogene GTPase (HRAS) for <1%. Several studies have reported an association between KRAS mutations, and poor prognosis of CRC, and lung and liver metastasis (20, 21). In contrast, several other studies reported that KRAS mutations were strong independent predictors of survival in patients with CRC. These contradictory findings may be explained by the differences in the distribution of specific KRAS mutations, stage at diagnosis or other characteristics (22). KRAS mutations have emerged as an important predictive marker of resistance to anti-epidermal growth factor receptors (EGFR) agents, including panitumumab and cetuximab. Activating KRAS mutations have been identified in 35–45% of CRC cases, and primarily occur in codon 12 and 13. KRAS mutation status is now firmly established as a predictive biomarker for treatment with EGFR inhibitors. A number of studies have established that the addition of cetuximab to first-line palliative chemotherapy can significantly prolong progression-free survival and overall survival in patients with KRAS wild-type CRC, but not in patients with KRAS-mutated disease (23, 24).

BRAF

The BRAF protooncogene, which encodes for the BRAF protein kinase, is located on chromosome 7 (q34) and is composed of 18 exons. BRAF mutations have been found in 7–10% of patients with metastatic CRC. This mutation more prevalent in proximal colon tumours and it rarely found in the left colon (25). Activating mutations in the BRAF gene (which codes for a serine-threonine kinase downstream of KRAS) have also been found in a number of different cancers, including CRC (26). Like KRAS mutation status, the role of BRAF as a prognostic biomarker in colon cancer remains unclear. However, like KRAS mutations, the presence of a BRAF mutation has also been shown to confer resistance to EGFR inhibitor therapy in CRC (5, 6, 27). Vemurafenib is a BRAF inhibitor that targets the BRAF V600E mutation, resulting in dramatic responses in patients with melanoma. Unfortunately, the effect of targeting BRAF in patients with CRC has, so far, been disappointing. In a phase I trial of single agent vemurafenib in patients with BRAF mutant CRC, only 1 of 19 patients had a partial response and 4 had minor responses (≥10% shrinkage). One possible explanation for the resistance to vemurafenib monotherapy in patients with BRAF-mutant CRC is that BRAF inhibition causes feedback activation of EGFR (28).

PI3K pathway

The main alterations in the PI3K pathway in CRC are mutations in PIK3CA and loss of PTEN protein expression. PTEN loss correlates with advanced and metastatic tumours and has been associated with worse survival outcomes in CRC (29). There is evidence that PIK3CA mutations also confer resistance to EGFR inhibitor therapy, both in vitro and in the clinical setting. PI3K inhibitors are now being developed and are in early-phase clinical trials (30). There is also preclinical evidence that combining MEK inhibitors and MTOR inhibitors (MTOR is a protein located in downstream of AKT, that involved in regulating cell growth and apoptosis) has a greater effect in suppressing cancer cell proliferation and inducing apoptosis in colorectal cancer cell lines and reducing tumor volume in mice models compared with single agent therapy (31).

Microsatellite instability (MSI)

Microsatellites are repeated DNA sequences, usually 1 to 10 nucleotides long, present throughout the genome. Instability is mostly characterized by single base-pair insertions or deletions in these repeat loci, causing widespread genomic instability due to the failure of the cell's mis- match repair (MMR) mechanism (32). This form of genomic instability occurs in approximately 15% of sporadic cases of CRC, as well as in patients with hereditary nonpolyposis CRC Nevertheless, patients with MSI may be suitable for targeted therapies that take advantage of the sensitivity of these tumours to drugs that cause specific types of DNA damage. For example, due to a synthetic lethal relationship, MSH2-defective tumours are highly sensitive to methotrexate and this is the focus of a current phase II trial (33). More robust clinical data is needed to determine if the MSI phenotype will be a useful prognostic and/or predictive biomarker. Overall, the benefit of 5-FU in the adjuvant treatment of stage III CRC is well established, but for stage II disease this is less clear. In the future, establishing the MSI status of a patient's tumor could play an important role in determining both prognosis and whether or not adjuvant 5-FU chemotherapy is likely to provide significant benefit (34).

Personalized medicine in CRC

Modern personalized medicine takes into account an individual's genetic makeup and disease history before a treatment regimen is administered. This is in contrast to traditional personalized medicine, in which care is provide of based on a patient's family history, social circumstances, environment, and lifestyle (35).

As we acknowledge the heterogeneity of CRC, the use of new tools helps us to identify these heterogeneous factors, we are closer to understand the personalized nature of CRC (36). Biomarker discovery has been vital in implementation of usage in clinics. Management of CRC uses biomarkers that could serve to predict the drug response in a patient. Moreover specific biomarkers helpful in designing the treatment modalities and monitoring the disease progression in patients serve as tools for personalized medicine (37). Genome-wide association studies (GWAS) have identified SNPs associated with the risk of development and progression of CRC and also correlated with therapeutic responses. These SNPs along with others may applied in personalized medicine; for example, testing patients for rs396991 SNPs may predicts therapeutic responses to drugs such as cetuximab. The development of predictive and prognostic biomarkers may allow an improved classification of CRC patients who would benefit the most from adjuvant chemotherapy at a particular stage of disease (37, 38).

Future perspective

Since personalized medicine works on three subjects of determining disease indices in people, choosing the best therapeutic method and predicting disease relapse. It seems more researches are required CRC to achieve favorable results (39). In the next few years, it is likely that molecular analysis of CRC specimens at diagnosis will become standard practice, with other tests such as gene-expression profiling and somatic mutation analysis helping to predict the risk of relapse, as well as

selecting which systemic therapies are most likely to be effective for each patients (40). Personalized medicine aimed towards preventing metastatic CRC, screening patients have already made good progress but is limited due to the overwhelming task of generating data for the entire population. Establishing the specific genetic profile of individual tumors will enable the use of a combining different targeted therapies, which likely reduce resistance and improve response to treatment and control of disease, thus reducing the mortality rate CRC patients (41).

CONCLUSION

CRC is one of the most common cancers worldwide. Today, various techniques are available to detect CRC in its early stages or as precursor lesions, thereby preventing aggressive treatment. With all chemotherapies or targeted therapies in CRC, the most critical factor in treating patients is to focus on early identification of and development of techniques that work on early diagnosis biomarkers (42). Personalized medicine has made some major advances in monitoring CRC, through KRAS nalysis now as a routine clinical practice. However, KRAS has some limitations as a biomarker and despite extensive research into other biomarkers for antiangiogenic drugs, chemotherapy and other targeted agents, they are not yet to be established in clinical practice (43, 44). Chemotherapy remains the cornerstone of systemic treatment today, but several new targeted treatment have emerged in this filed in the last decade, improving the management of metastatic disease (45). The recent advances in molecular biology and the genetic classification of CRC are essential to individualize these therapies and will be a foundation for improving the treatment in the future (46).

REFERENCES

1.Adams, Richard A., et al. “Epiregulin (EREG) and amphiregulin (AREG) gene expression to predict response to cetuximab therapy in combination with oxaliplatin (Ox) and 5FU in first-line treatment of advanced colorectal cancer (aCRC).” (2012): 3516-3516.

2.Alymani NA, Smith MD, Williams DJ, Petty RD. Predictive biomarkers for personalised anti-cancer drug use: discovery to clinical implementation. European Journal of Cancer. 2010 Mar 1;46(5):869-79.

3.Amado, Rafael G., et al. “Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer.” (2008): 1626-1634.

4.Baker JB, Dutta D, Watson D, Maddala T, Munneke BM, Shak S, Rowinsky EK, Xu LA, Harbison CT, Clark EA, Mauro DJ. Tumour gene expression predicts response to cetuximab in patients with KRAS wild-type metastatic colorectal cancer. British journal of cancer. 2011 Feb;104(3):488-95.

5.Baldus SE, Schaefer KL, Engers R, Hartleb D, Stoecklein NH, Gabbert HE. Prevalence and heterogeneity of KRAS, BRAF, and PIK3CA mutations in primary colorectal adenocarcinomas and their corresponding metastases. Clinical Cancer Research. 2010 Feb 1;16(3):790-9.

6.Safaei A, Sobhi S, Rezaei-Tavirani M, Zali MR. Genomic and epigenetic instability in colorectal cancer. Iran J Cancer Prev. 2013;6:54-63.

7.Blanco-Calvo M, Concha Á, Figueroa A, Garrido F, Valladares-Ayerbes M. Colorectal cancer classification and cell heterogeneity: a systems oncology approach. International journal of molecular sciences. 2015 Jun;16(6):13610-32.

8.Rezaie-Tavirani M, Fayazfar S, Heydari-Keshel S, Rezaee MB, Zamanian-Azodi M, Rezaei-Tavirani M, Khodarahmi R. Effect of essential oil of Rosa Damascena on human colon cancer cell line SW742. Gastroenterology and Hepatology from bed to bench. 2013;6(1):25.

9.Ewing I, Hurley JJ, Josephides E, Millar A. The molecular genetics of colorectal cancer. Frontline gastroenterology. 2014 Jan 1;5(1):26-30.

10.Lao VV, Grady WM. Epigenetics and colorectal cancer. Nature reviews Gastroenterology & hepatology. 2011 Dec;8(12):686-700.

11.Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. International journal of cancer. 2010 Dec 15;127(12):2893-917.

12.Sobin LH, Gospodarowicz MK, Wittekind C, editors. TNM classification of malignant tumours. John Wiley & Sons; 2011 Aug 31.

13.Chan GH, Chee CE. Making sense of adjuvant chemotherapy in colorectal cancer. Journal of gastrointestinal oncology. 2019 Dec;10(6):1183.

14.Ranieri G, Laface C, Laforgia M, De Summa S, Porcelli M, Macina F, Ammendola M, Molinari P, Lauletta G, Di Palo A, Rubini G. Bevacizumab plus FOLFOX-4 combined with deep electro-hyperthermia as first-line therapy in metastatic colon cancer: A pilot study. Frontiers in Oncology. 2020 Nov 3;10:2387.

15.Baraniskin A, Buchberger B, Pox C, Graeven U, Holch JW, Schmiegel W, Heinemann V. Efficacy of bevacizumab in first-line treatment of metastatic colorectal cancer: a systematic review and meta-analysis. European Journal of Cancer. 2019 Jan 1;106:37-44.

16.Lugli A. Towards a molecular classification of colorectal cancer. Frontiers in oncology. 2015 Feb 25;5:46.

17.Sinicrope FA, Okamoto K, Kasi PM, Kawakami H. Molecular biomarkers in the personalized treatment of colorectal cancer. Clinical Gastroenterology and Hepatology. 2016 May 1;14(5):651-8.

18.Zocche DM, Ramirez C, Fontao FM, Costa LD, Redal MA. Global impact of KRAS mutation patterns in FOLFOX treated metastatic colorectal cancer. Frontiers in genetics. 2015 Mar 30;6:116.

19.Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. cell. 1990 Jun 1;61(5):759-67.

20.Ma H, Brosens LA, Offerhaus GJ, Giardiello FM, de Leng

WW, Montgomery EA. Pathology and genetics of hereditary colorectal cancer. Pathology. 2018 Jan 1;50(1):49-59.

21. Schatoff EM, Goswami S, Zafra MP, Foronda M, Shusterman M, Leach BI, Katti A, Diaz BJ, Dow LE. Distinct colorectal cancer–associated apc mutations dictate response to tankyrase inhibition. Cancer discovery. 2019 Oct 1;9(10):1358-71.

22. Aghababa, Amirhossein Akbari, and Tarun Kumar. "The Importance of Personalized medicine in Colorectal Cancer." gene expression 6 (2021): 7.

23.Bertotti A, Migliardi G, Galimi F, Sassi F, Torti D, Isella C, Corà D, Di Nicolantonio F, Buscarino M, Petti C, Ribero D. A molecularly annotated platform of patient-derived xenografts ("xenopatients") identifies HER2 as an effective therapeutic target in cetuximab-resistant colorectal cancer. Cancer discovery. 2011 Nov 1;1(6):508-23.

24.Blanke CD, Goldberg RM, Grothey A, Mooney M, Roach N, Saltz LB, Welch JJ, Wood WA, Meropol NJ. KRAS and colorectal cancer: ethical and pragmatic issues in effecting real-time change in oncology clinical trials and practice. The oncologist. 2011 Aug;16(8):1061.

25.Bokemeyer C, Bondarenko I, Makhson A, Hartmann JT, Aparicio J, De Braud F, Donea S, Ludwig H, Schuch G, Stroh C, Loos AH. Fluorouracil leucovorin and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. American Society of Clinical Oncology.

26.Pritzker KP, Pritzker LB. Bioinformatics advances for clinical biomarker development. Expert opinion on medical diagnostics. 2012 Jan 1;6(1):39-48.

27.Monzon FA, Ogino S, Hammond ME, Halling KC, Bloom KJ, Nikiforova MN. The role of KRAS mutation testing in the management of patients with metastatic colorectal cancer. Archives of pathology & laboratory medicine. 2009 Oct;133(10):1600-6.

28.Pander J, Gelderblom H, Antonini NF, Tol J, van Krieken JH, van der Straaten T, Punt CJ, Guchelaar HJ. Correlation of FCGR3A and EGFR germline polymorphisms with the efficacy of cetuximab in KRAS wild-type metastatic colorectal cancer. European journal of cancer. 2010 Jul 1;46(10):1829-34.

29.Qian W, Feng Y, Li J, Peng W, Gu Q, Zhang Z, Ji D, Wang Q, Zhang D, Sun Y. Construction of ceRNA networks reveals differences between distal and proximal colon cancers. Oncology reports. 2019 May 1;41(5):3027-40.

30.Mori Y, Kudo SE, Misawa M, Takeda K, Kudo T, Itoh H, Oda M, Mori K. How Far Will Clinical Application of AI Applications Advance for Colorectal Cancer Diagnosis?. Journal of the anus, rectum and colon. 2020 Apr 28;4(2):47-50.

Chatterjee K, Mukherjee P, Hoque J, Das M, Saha S. Extended RAS mutations (KRAS and NRAS) in patients with colorectal cancers in eastern India: An observational study. Cancer Research, Statistics, and Treatment. 2021 Apr 1;4(2):244.

32. Charlton ME, Kahl AR, Greenbaum AA, Karlitz JJ, Lin C, Lynch CF, Chen VW. KRAS testing, tumor location, and survival in patients with stage IV colorectal cancer: SEER 2010–2013. Journal of the National Comprehensive Cancer Network. 2017 Dec 1;15(12):1484-93.

33.Karapetis CS, Khambata-Ford S, Jonker DJ, O'Callaghan CJ, Tu D, Tebbutt NC, Simes RJ, Chalchal H, Shapiro JD, Robitaille S, Price TJ. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. New England Journal of Medicine. 2008 Oct 23;359(17):1757-65.

34.de la Fouchardière C, Cohen R, Malka D, Guimbaud R, Bourien H, Lièvre A, Cacheux W, Artru P, François E, Gilabert M, Samalin-Scalzi E. Characteristics of BRAFV600E mutant, deficient mismatch repair/proficient mismatch repair, metastatic colorectal cancer: A multicenter series of 287 patients. The oncologist. 2019 Dec;24(12):e1331.

35.Jover R, Zapater P, Castells A, Llor X, Andreu M, Cubiella J, Piñol V, Xicola RM, Bujanda L, Reñé JM, Clofent J. Mismatch repair status in the prediction of benefit from adjuvant fluorouracil chemotherapy in colorectal cancer. Gut. 2006 Jun 1;55(6):848-55.

36.Knapen DG, Cherny NI, Zygoura P, Latino NJ, Douillard JY, Dafni U, de Vries EG, de Groot DJ. Lessons learnt from scoring adjuvant colon cancer trials and meta-analyses using the ESMO-Magnitude of Clinical Benefit Scale V. 1.1. ESMO open. 2020 Jan 1;5(5):e000681.

37.Codes AP. Medical Oncology Services: Colon Cancer; Neoadjuvant or Adjuvant Therapy. POLICY. 2019;7:158.

38.Ma Y, Zhang P, Wang F, Liu W, Yang J, Qin H. An integrated proteomics and metabolomics approach for defining oncofetal biomarkers in the colorectal cancer. Annals of surgery. 2012 Apr 1;255(4):720-30.

39.Ogino S, Fuchs CS, Giovannucci E. How many molecular subtypes? Implications of the unique tumor principle in personalized medicine. Expert review of molecular diagnostics. 2012 Jul 1;12(6):621-8.

40. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. cell. 1990 Jun 1;61(5):759-67.

41.Gustavsson B, Carlsson G, Machover D, Petrelli N, Roth A, Schmoll HJ, Tveit KM, Gibson F. A review of the evolution of systemic chemotherapy in the management of colorectal cancer. Clinical colorectal cancer. 2015 Mar 1;14(1):1-0.

42.Sebio A, Stintzing S, Stremitzer S, Zhang W, Lenz HJ. Panitumumab: leading to better overall survival in metastatic colorectal cancer?. Expert opinion on biological therapy. 2014 Apr 1;14(4):535-48.

43.Saridaki Z, Souglakos J, Georgoulias V. Prognostic and predictive significance of MSI in stages II/III colon cancer. World Journal of Gastroenterology: WJG. 2014 Jun 14;20(22):6809.

44.Gonzalez-Pons M, Cruz-Correa M. Colorectal cancer biomarkers: where are we now?. BioMed research international. 2015 Oct;2015.

45.Newton KF, Newman W, Hill J. Review of biomarkers in colorectal cancer. Colorectal disease. 2012 Jan;14(1):3-17.

46.Ramos E, Callier SL, Rotimi CN. Why personalized medicine will fail if we stay the course. Personalized medicine. 2012 Nov;9(8):839-47.