Aloha International Journal of Health Advancement (AIJHA)
ISSN 2621-8224
Volume 5 Number 8, August 2022 RESEARCH
http://journal.aloha.academy/index.php/aijha DOI: http://dx.doi.org/10.33846/aijha50801

Mutations in the p53 Gene in Colorectal Cancer

Hevi Horiza[1(corresponding author)], Iwan Iskandar[2], Mutia Yuhesti[3]
1Department of Environmental Health, Potekkes Kemenkes Tanjungpinang, Indonesia;
hevi220987@gmail.com
2Department of Environmental Health, Potekkes Kemenkes Tanjungpinang, Indonesia;
iwan_kkp_tpi@yahoo.com
[3]Department of Environmental Health, Potekkes Kemenkes Tanjungpinang, Indonesia;
mutia08yuhesti@gmail.com

Submitted: August 2, 2022 -Revised: August 22, 2022 -Accepted: August 28, 2022 -Published: August 31, 2022

ABSTRACT

Colorectal cancer is the second leading cause of death, which can be caused by diet, lifestyle, the presence of genes that play a role in the cell cycle and its relationship to the cancer growth process, such as groups that trigger tumors (tumor oncogenes) such as race genes and tumor suppressor such as the p53 gene. One of the causes of colorectal cancer is mutation and allelic loss of the p53 gene. Mutations in the p53 gene mostly occur in conserved areas, namely in the exon 5-9 region, and there are also found in areas outside the exon 5-9 region. Efforts to treat and prevent colorectal cancer are chemotherapy and improving diet by consuming fiber-rich foods.
Keywords: colon; colorectal cancer; p53 gene mutation; treatment

INTRODUCTION

Colorectal cancer is the fourth malignancy worldwide, with an estimated 1,023,000 cases and 529,000 deaths each year. In the United States, this cancer ranks third malignancy [(1)]. In Canada, colorectal cancer is the second leading cause of death, and in 2006 there were 20,000 cases and 8500 deaths [(2)]. Of all the types of cancer that exist, colorectal cancer is the second leading cause of death, with slightly more men than women with a ratio of 19.4 and 15.3 per 100,000 population [(3)]. This cancer is most commonly found in North America, Australia, New Zealand and parts of Europe (Western Europe which has entered the category of developed countries). Colorectal cancer is a serious problem in Indonesia. The number of cancer patients ranks 10th (2.75%), after cervical cancer, breast, lymph node, skin, nasopharynx, ovary, rectum, soft tissue and thyroid [(4)].

The incidence of colorectal cancer nationally does not yet exist. In 14 provinces in Indonesia, 1378 cases of colorectal cancer were found out of a total population of 134,743,420 or 1.8 per 100,000 population [(1)]. Based on data from the Central General Hospital (RSUP) M. Jamil Padang, in 2007 it was known that there were 238 colorectal cancer patients.

The high percentage of colorectal cancer sufferers is caused by an instant lifestyle. Modern life which offers a lot of convenience and speed in meeting one's needs has had an impact on changing the lifestyle of some people. The number of fast food and high-fat foods, which causes some people to be less interested in consuming natural foods that take a long time to process.

Cancer can be caused by external factors and internal factors. The main internal factor is the presence of genes that play a role in the cell cycle has become the center of attention in relation to the process of cancer growth. In relation to cancer growth, there are two groups of genes. The first is the group that triggers the occurrence of tumors commonly called tumor oncogenes such as the race gene; the second is a group that suppresses the occurrence of tumors commonly called tumor suppressor genes, such as the p53 gene [(5)].

The p53 gene is a tumor suppressor gene that has a molecular weight of 53 kilodaltons (kD). The p53 gene which is a transcription factor is located on the human chromosome 17p13.1, consisting of 393 amino acids, 11 exons and has a length of 20 kilobases. To carry out its function, p53 binds to DNA in a specific form that allows p53 to activate the transcription of target genes. The central part of this protein (amino acid residues 102-292) is a specific DNA-binding region, where spontaneous p53 mutations in this region directly or indirectly affect the interaction of p53 with DNA [(6)]. One of the causes of colorectal cancer is mutation and allelic loss of the p53 gene [(7)]. Mutations in the p53 gene cause a loss of function of p53 as a regulator of abnormal cell development and death [(8)].

Research on colorectal cancer that has been carried out includes Overexpression of p53 mRNA in Colorectal Cancer and its Relationship to p53 Gene Mutation. The results of this study showed that from 109 patients with colorectal cancer at the Hospital Saint-Antoine France, the expression of mutations at the mRNA level of the p53 gene contained three point mutations that caused stop codons at codons 148, 186 and 193. Nine mutations at codon 273, six base changes from CGT→TGT and three base changes from CGT→ CAT. Six mutations at codon 248 four base changes from CGG→CAG and two base changes from CGG→TGG. Two mutations at codon 175 are

Aloha International Journal of Health Advancement (AIJHA)
ISSN 2621-8224
Volume 5 Number 8, August 2022 RESEARCH
http://journal.aloha.academy/index.php/aijha DOI: http://dx.doi.org/10.33846/aijha50801

base changes from CGC→CAC and CGC→TGC and mutations at codon 245 are base changes from GGC→GGA and GGC→TGC. Two more mutations occur at codon 272, namely base changes from GTG→ATG and GTG→TTG [7].

Another study is Ki-ras Mutation and p53 Overexpression Predict the Clinical Behavior of Colorectal Cancer: A Southwest Oncology Group Study. The results of this study showed that 40% of the Ki-ras oncogene mutations occurred at codons 12 and 13 in colon cancer and single mutations at codons 14,15 and 19 [9].

Another study that has been done on colorectal cancer is Mutations and Allelic Loss of p53 in Primary Tumor DNA From Potentially Cured Patients With Colorectal Carcinoma. The results of this study indicate that there are 29 patients who have the potential to suffer from stage one colorectal cancer in the United States. The average age of these patients was 61 years. 15 patients (52%) indicated that the cancer site was in the colon and 14 patients (48%) had the cancer site in the rectum. Of the 25 colonic tissues of patients known to have colorectal cancer, 15 (60%) of them had mutations in exon 5-9. Four (16%) of the 25 patients had two mutations. Of the 19 mutations, four (21%) were in exon 5, two (11%) were in exon 6, three (16%) were in exon 7 and ten (53%) were in exon 8 [10].

Research on the p53 gene in colorectal cancer for the Asian region is TP53 Pro47Ser and Arg72Pro polymorphisms and colorectal cancer predisposition in an ethnic Kashmiri population. This study provides information that there are two polymorphisms that occur in colorectal cancer patients in Kashmir, India for the TP53 protein, namely codon 47 (TP53 Pro47Ser) and codon 72 (TP53 Arg72Pro) [11].

COLON

Intestinum crassum (large intestine) is divided into caecum, vermiform appendix, ascending colon, transverse colon, descending colon, sigmoid colon; rectum and anal canal. The ascending colon is about 5 inches (13 cm) long and extends upward from the cecum to the inferior surface of the right lobe of the liver, then the ascending colon bends to the left, forming the right coli flexure. The transverse colon is about 15 inches (38 cm) long and runs across the abdomen, occupying the umbilical region. The transverse mesocolon is attached to the superior border of the transverse colon, and the posterior layer of the greater omentum is placed on the inferior border. Because the transverse mesocolon is very long, the position of the transverse colon varies widely and can reach the pelvis. The descending colon is 10 inches (25 cm) long and is located in the left upper and lower quadrants. This colon runs downward from the left coli flexure to the pelvic rim, where the transverse colon continues to become the sigmoid colon [12].

The large intestine has various functions, all of which are related to the final process of intestinal contents. The most important function of the large intestine is the absorption of water and electrolytes, which mostly takes place in the right colon. The sigmoid colon functions as a reservoir for dehydration of the fecal mass until defecation takes place [13].

The colon absorbs about 600 mL of water per day, but the absorption capacity of the large intestine is 2000 mL per day. Excessive fluid delivery from the ileum can result in diarrhea. The final weight of feces excreted per day is about 200 g, 75% of which is water. The remainder consists of unabsorbed food residues, bacteria, sloughed epithelial cells, and unabsorbed minerals. Very little digestion takes place in the large intestine. The secretions of the large intestine contain a lot of mucus, exhibit an alkyl reaction and do not contain enzymes. Mucus acts as a lubricant and protects the mucosa. In inflammatory bowel conditions, the excessive increase in mucus secretion may be responsible for protein loss in feces [13].

COLORECTAL CANCER

Many factors cause cancer, both external and internal. Internal factors, especially the presence of genes that play a role in the cell cycle, have become the center of attention in relation to the process of tumor growth. In relation to tumor growth, there are two groups of genes: first is the group that triggers the occurrence of tumors commonly called tumor oncogenes such as the c-myc gene and the ras gene; the second is a group that suppresses the occurrence of tumors commonly called tumor suppressor genes such as the p53 gene and the Rb gene [5].

Cancer is the main problem in the medical field and is one of the top 10 causes of death in the world, and is a malignant disease that can cause death in sufferers because cancer cells damage other cells. Cancer cells are normal cells that undergo mutations or genetic changes and grow without being coordinated with the growth of cells. The process of cancer formation (carcinogenesis) is a somatic event and has long been thought to be caused by the accumulation of genetic and epigenetic changes that cause changes in the normal molecular control settings of cell proliferation. These genetic changes can be in the form of activation of proto-oncogenes or inactivation of tumor suppressor genes that can trigger tumorigenesis and increase its progression [6].

Colorectal cancer is the fourth most common cancer in the world that causes death. Based on a report from the magazine "*Cermin Dunia Kedokteran*" it is stated that there are 1,023,000 cases of colorectal cancer with an

Aloha International Journal of Health Advancement (AIJHA)
ISSN 2621-8224
Volume 5 Number 8, August 2022 RESEARCH
http://journal.aloha.academy/index.php/aijha DOI: http://dx.doi.org/10.33846/aijha50801

annual mortality rate of 529,000 [1]. Based on Medicinus, of all types of cancer, colorectal cancer is the second leading cause of death and ranks 4th in the world, with the number of male patients slightly more than women with a ratio of 19.4 and 15.3 per 100,000 population [3].

Colorectal cancer can be caused by several factors including: age, the risk of developing colorectal cancer increases with age. This case mostly occurs in the 60-70s, and rarely occurs under the age of 50 years unless there is a family history of colorectal cancer; the presence of polyps in the colon, especially adenomatous polyps; a history of cancer, a person who has been diagnosed with or has been treated for colon cancer is at risk for developing colon cancer in the future. Women who have had ovarian cancer (ovary), uterine cancer and breast cancer have a greater risk of developing colorectal cancer; hereditary factors such as a history of colon cancer, especially close relatives, FAP (Familial Adenomatous Polyposis) - Familial Adenomatous Polyps (occurring in families) have a 100% risk of developing colorectal cancer before the age of 40 years, if not treated, other diseases in the family, such as HNPCC (Hereditary Non Polyposis Colorectal Cancer) – non-polyp colorectal cancer that runs in families or Lynch syndrome; untreated ulcerative colitis; smoking habits, smokers have a much greater risk of developing colorectal cancer; eating habits, it has been studied that the habit of eating lots of meat and little fruit, vegetables, and fish also increases the risk of colorectal cancer; little activity, people who do more physical activity have a lower risk of developing colorectal cancer; viral infection, certain viruses such as HPV (Human Papilloma Virus) contribute to the occurrence of colorectal cancer [14].

The discovery of molecular genetics has made it possible for hereditary colorectal cancers to be divided into two groups [15]:

1. Tumors showing microsatellite instability, occurring more frequently in the right colon, having diploid DNA, harboring characteristic mutations (eg altered growth factor receptor type II and BAX or Hereditary non polypopsis colorectal cancer).
2. Tumors with chromosomal instability that tend to be in the left colon, their DNA shows aneuploidy harboring mutations characteristic of K-ras, APC and the polypopsis-FAP p53 gene family.

TUMOR SUPPRESSOR GENES

Tumor suppressors are cell guardians against DNA damage, induced by ultraviolet (UV) exposure to sunlight, gamma radiation, X-rays, chemotherapy drugs, or excess inappropriate proliferation signals. They prevent new cells from becoming malignant by arresting their proliferation or persuading them to commit suicide (apoptotic cell death). Tumor suppressors monitor critical cellular checkpoints that regulate the mitotic cycle, DNA repair, transcription, apoptosis, and differentiation. Some tumor suppressors prevent the activation of inappropriate signaling pathways involved in cell growth. Functional inactivation of tumor suppressors is by mutation, deletion (deletion), or silencing of genes that create imbalances between cells, death and differentiation of proliferative programs that facilitate tumorigenesis (figure 1) [16].

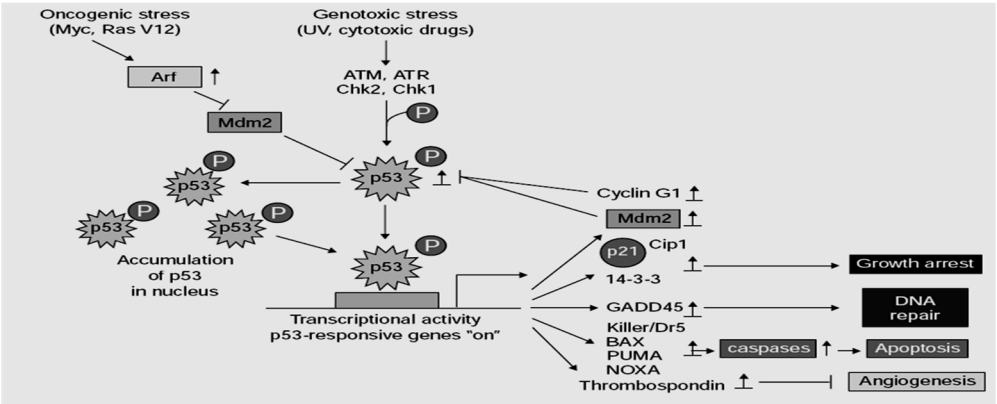

Figure 1. Activation and function of p53 [16]

Some rare individuals are born with mutations in tumor suppressor genes that can predispose them to developing cancer. Tumor suppressors, to date, represent about 0.001% (30) of the total number of genes (approximately 30,000) that make up the entire mammalian genome. This number may increase as new technologies are used to study cancer cells. It is now clear that tumor suppressor cells have evolved as part of several complex defense systems against cell proliferation. As the name suggests, tumor suppressors are proteins that regulate cell proliferation by eliminating cells that are damaged (by cellular stress such as UV, X-rays, chemotherapy drugs) or that multiply abnormally in response to hyperproliferative signals. All mammalian cells

Aloha International Journal of Health Advancement (AIJHA)
ISSN 2621-8224
Volume 5 Number 8, August 2022 RESEARCH
http://journal.aloha.academy/index.php/aijha DOI: http://dx.doi.org/10.33846/aijha50801

express at least some tumor suppressors and thus play an important role in cancer prevention [16]. Some of the tumor suppressors found in the human body are presented in Table 1.

Table 1. Some tumor suppressors [16]

Gene	Nomenclature	Function	Chromosome location (human)	Tumor type
RBI P53/TP53	Retinoblastoma	Cell cycle regulator, apoptosis regulator, haploinsufficient	13q14-q14.2 17p13.1	Retinoblastoma, sarcomas lymphomas, sarcomas, brain and breast cancers
CDKN2A/ INK4A	Cyclin- dependent kinase inhibitory protein $p16^{Ink4a}$	Cell cycle regulator	9p21	Melanoma, many cancers
CDKN2A/ ARF	Alternative reading frame	Cell cycle regulator	9p21	Sarcomas, lymphomas, many cancers
Tob1		Transcriptional corepressor		Liver cancers
APC	Adenomatous polyposis (Familial)	Signaling	5q21-q22	Colon cancer
BRCA1	Breast cancer (Familial)	DNA repair	17q21	Breast and ovarian cancer
BRCA2	Breast cancer (familial)	DNA repair	13q12.3	Breast and ovarian cancer
CDKN2C/ INK4C	Cyclin- dependent kinase inhibitory protein $p18^{Ink4c}$	Cell cycle regulator, haploinsufficient	1p21	Testicular cancer
CDKN1B/ KIP1	Cyclin- dependent kinase inhibitory protein $p27^{Kipl}$	Cell cycle regulator, haploinsufficient	17p	Breast, prostate, many cancers
MSH2	Nonpolyposis colon cancer (hereditary)	DNA mismatch repair	2p22-p21	Colon cancer
MLH1	Nonpolyposis colon cancer (hereditary)	DNA mismatch repair	3p21.3	Colon cancer
VHL	Von Hippel- Lindau syndrome	Transcription elongation	3p26-p25	Renal cancers, hemangioblastoma, pheochromocytoma

The second category of genes that play a role in the development of cancer are those that when working normally can suppress the development of malignancy. Some cancers arise as a result of malfunctioning of the regulatory protein for which this gene is encoded. One of the proteins that function as a regulatory protein or suppressor protein is p53 [17]. The p53 tumor suppressor gene is a protein with a molecular weight of 53 kilodaltons (kD) and was first discovered in 1979. The p53 gene, which is a transcription factor, is located on the human chromosome 17p13.1, consisting of 393 amino acids, 11 exons, and a length of 20 kilobase [6].

The p53 gene is a cell cycle protector. When a cell is injured, p53 in the nucleus triggers the cell to "arrest" the G1 and S border region by inducing a CDK inhibitor (Cyclin D Kinase) and the most advanced DNA repair system removes the wound before the cell enters the S phase in the absence of injured DNA (Figure 2). This "arrest" and apoptosis program depends on the physiological environment or cell type. Therefore, the loss of function of this p53 gene is the cause of the emergence of maglination. This p53 gene inactivation usually occurs in two stages, namely the inactivation of one allele by a point mutation or small deletion and the next is the loss of the normal allele by deletion of a chromosomal segment [6].

During their lifetime, normal cells are constantly exposed to various endogenous and exogenous stresses that can change their normal character which involves genetic changes. Genetic changes that can cause mutations are very harmful to the cells of the offspring and lead to the formation of neoplasia. The TP53 protein encoded by the p53 gene functions as a tetrametric transcription factor found at very low levels in unstressed cells (figure 3). After stress, various pathways are carried out towards post-translational modification of the protein and its stabilization. This accumulation activates the transcription of a large number of genes involved in various activities within the cell including cell cycle inhibition and apoptosis depending on the cellular context, wound size, or other unknown parameters. The p53 mutation is the most common genetic alteration found in human cancers and p53 function is lost indirectly either by nuclear exclusion, interaction with viral proteins as in cervical cancer, or through its interaction with overexpression of the mdm2 protein [6].

Aloha International Journal of Health Advancement (AIJHA)
ISSN 2621-8224
Volume 5 Number 8, August 2022 RESEARCH
http://journal.aloha.academy/index.php/aijha DOI: http://dx.doi.org/10.33846/aijha50801

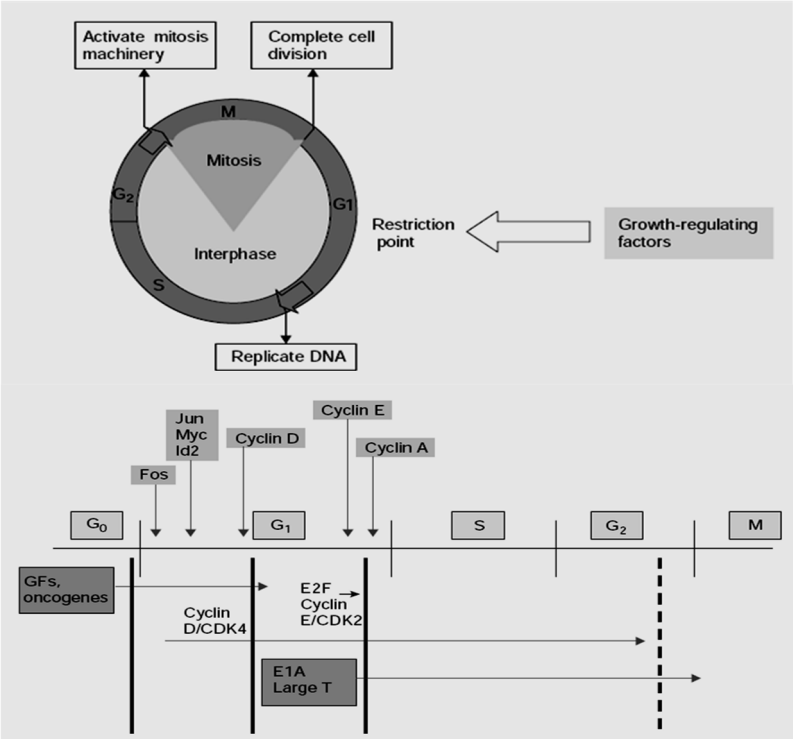

Figure 2. Cell Cycle [16]

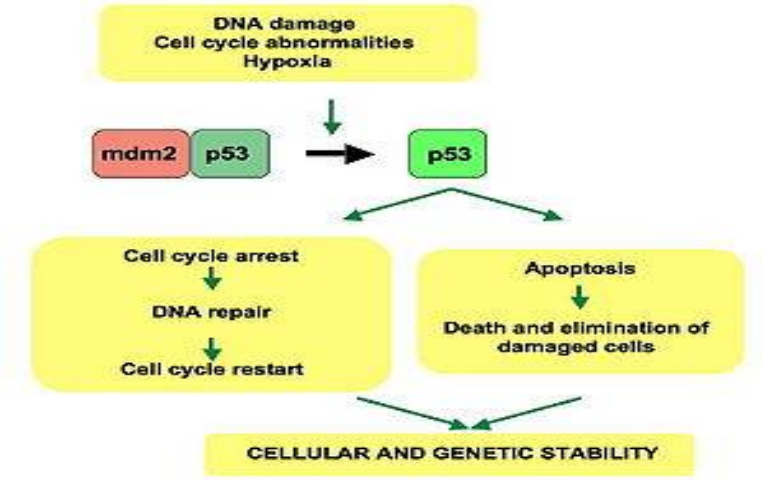

Figure 3. Pathway of p53

Mutations in the p53 gene can occur in the conserved region and outside the conserved region. However, mutations in conserved areas were 89% greater than mutations in areas outside conserved 11%. Mutations that occur in the p53 gene vary from the exon 5-9 region. Amino acids that change due to mutations in the p53 gene include Lys → Gln, Arg → His, Arg → stop and Arg → Trp [10].

Based on research data on colorectal cancer in France, the p53 gene mutations that occurred were 36 substitutions of 1 base pair, 28 (77.8%) of which were transitions G:C ← → A:T and 8 (22.2%) were transversions. 3 point mutations that produce stop codons are at codons 148, 186 and 193.33 of 44 (75%) mutations detected are at codons 175, 245, 248, 273, and 272 which are common areas of mutation in colorectal cancer. 9 of the mutations were centered at codon 273 (6 changes from CGT→TGT and 3 changes from CGT→CAT, R→H). 6 mutations occurred at codon 248 (4 changes in CGG→CAG, R→Q and 2 changes in CGG→TGG, R→W). two mutations occurred at codon 175 (CGC→CAC, R→H and CGC→GGC, R→G) and at codon 245 (GGC→GGA, G→D and GGC→TGC, G→C). two mutations at codon 272 (GTG→ATG, V→M and GTG→TTG, V→L). The deletions

Aloha International Journal of Health Advancement (AIJHA)
ISSN 2621-8224
Volume 5 Number 8, August 2022 RESEARCH
http://journal.aloha.academy/index.php/aijha DOI: http://dx.doi.org/10.33846/aijha50801

that occur are cytosine 983 at codon 257 tumor tissue 147, adenine 1052 at codon 280 tumor tissue 164, and cytosine 1115 at codon 301 tumor tissue 9 [7].

Table 2. Mutations in the p53 gene in colorectal cancer that have been studied

No	Number of patients	Location	Codon	Canged base	Source
1	29	Colon & rectum	132, 175, 273, 196, 213 dan 248	AAG→CAG CGC→CAC CGT→CAT CGA→TGA CGA→CGG CGG→TGG	Forslund, A. et al. [10]
2	36	Colon & rectum	143, 161, 167, 168, 175, 179, 194, 196, 205, 220, 245, 248, 255, 257, 259, 263, 266, 272, 273, 274, 280, 301, 306	GTG→GCG GTG→GAG GCC→ACC CAG→CGG CAC→CGC CGC→CAC CGC→GGC CAT→TAT CTT→CCT CGA→TGA TAT→GAT TAT→TGT GGC→GAC GGC→TGC CGG→CAG CGG→TGG CGG→CAG ATC→TTC CTG→TG GAC→GTAC GGA→GTA GTG→ATG CGT→TGT CGT→CAT GTT→CTT AGA→GA CCA→CA CGA→TGA	El-Mahdani, N; et al. [7]
3	68	Colon & rectum	248, 195, 273, 158, 238, 249, 155, 174, 141, 151, 158, 204, 206, 244, 249, 272, 282, 192, 213, 152, 196, 220, 255, 256, 253, 201, 152, 202, 174, 177, 193, 242, 206, 207,	CGG→TGG ATC→TTC CGT→CAT CGC→CAC TGT→TAT AGG→AG ACC→AC AGG→AAG TGC→TAC CCC→TCC CGC→CAC GAG→TAG TTG→TAG GGC→AGC TGC→CGC CAG→TAG CGA→CGG CGG→TGG CGA→CTGA TAT→TGT ACT→AT ACC→AC ATC→A-C TTG→TTC CCG→CCCC CGT→CGTC CGG→CAG CCC→CC CAT→CAAT	Russo, A. et al. [18]

Aloha International Journal of Health Advancement (AIJHA)
ISSN 2621-8224
Volume 5 Number 8, August 2022 RESEARCH
http://journal.aloha.academy/index.php/aijha DOI: http://dx.doi.org/10.33846/aijha50801

COLORECTAL CANCER THERAPY OR TREATMENT

One of the treatments for colorectal cancer is chemotherapy. Since the early 1960s, where for the first time 5-fluorouracil (5-FU) was discovered and considered beneficial for CRC sufferers, chemotherapy for this cancer consisted only of a combination of 5-fluorouracil (5-FU), levamisole (later replaced with folinic acid or leucovorin) in a protocol known as FUFA, and this protocol has not changed for 40 years. Reports vary between different routes of administration, with a maximum life expectancy of 11 to 13 months. This causes colorectal cancer to "lag behind" other types of cancer in the progress of treatment. It was not until 1998 that Saltz reported irinotecan, purified from pine bark, as a new drug which, when added to the FUFA protocol, was followed by oxaliplatin, a platinum-based drug. These discoveries have occurred very quickly, followed by capecitabine and various biologic drugs (all in less than five years), so that clinicians are busy conducting studies to assess their effectiveness [(3)].

Irinotecan is a semisynthetic derivative of the natural alkaloid camptothecine which is converted to SN-38113 by the enzyme carboxylase. By inhibiting topoismerase-I, an enzyme that catalyzes DNA replication, it causes fragmentation and apoptosis of these cancer cells. Randomized studies have shown improvement in time to progression (progression free survival) in overall survival when irinotecan is added to a protocol containing 5-FU, either by infusion (FOLIFIRI) or bolus (IFL) [(3)].

Recently, it was discovered that this protocol resulted in a better life expectancy than the addition of capecitabine (CAPIRI or XELIRI) so that infusion therapy became the more widely accepted method [(3)].

In addition to the prevention and treatment of colorectal cancer can also be done by eating foods rich in fiber. When people consume a small amount of fibrous food, the stool that forms in the large intestine is small and has a hard texture. This form of stool causes the concentration of carcinogenic substances that may be in it to be concentrated (high concentration), while the small form of feces with a hard texture causes the transit of food (the time it takes from eating to being excreted as feces) to be long. As a result, there will be contact between carcinogens, in high concentrations and for a long time, with the colon wall which can lead to the formation of cancer cells [(19)].

Dietary fiber has a high water absorption capacity. The presence of dietary fiber in feces causes feces to absorb a lot of water so that the volume becomes large and the texture becomes soft. The presence of a large volume of feces will accelerate intestinal contractions for faster bowel movements – faster food transit time. A large volume of feces with a soft texture can dilute the carcinogenic compounds contained in it, so the concentration is much lower. Thus there will be contact between carcinogenic substances with low concentrations with the large intestine, and this contact also occurs in a shorter time, so it does not allow the formation of cancer cells [(19)].

CONCLUSION

From the description above, several conclusions can be drawn including: colorectal cancer is caused by two factors, namely internal factors and external factors. One of the internal factors that cause colorectal cancer is a mutation that occurs in the tumor suppressor gene, namely the p53 gene. Mutations in the p53 gene generally occur in the exon 5-9 region, sometimes outside this region.

REFERENCES

1. Santosa CS. Epidermal Growth Factor Receptor (EGFR) Sebagai Sasaran Terapi Kolorektal. Cermin Dunia Kedokteran. 2009;39(1):5-12.
2. Zarychanski R, Yue C, Charles NB, Paul CH. Frequency of Colorectal Cancer screening and the Impact of Family Physicians on Sreening Behaviour. CMAJ. Canadian Medical Association or its Licensos. 2007;177(6):593-598.
3. Aru WS. Apakah Oxaliplatin atau Irinotecan yang Digunakan Sebagai Terapi Ajuvan Kanker Kolorektal? Sebuah Perjalanan Sejarah Dalam Kemoterapi Kanker Usus Besar. Medicinus Scientific Journal of Pharmaceutical Development and Medical Application. 2010;23(2):4-6.
4. Anonymous. 2020. [cited 2020 Aug 2]. Available from: http://www.indonesia.com
5. Adi P, Ruben D, Istar Y, Ambar M. Ekspresi Protein p53, Rb, dan c-myc pada Kanker Serviks Uteri dengan Pengecatan Immunohistokimia. Biodiversitas. 2005;6(3):157-159.
6. Mukh S. Gen Penekan Tumor p53, Kanker dan Radiasi Pengion. Buletin Alara. 2007;8(3):119-128.
7. El-Mahdani N, Vailant JC, Guiget M, Prevot S, Bertrand V, Bernard C; Parc R, Bereziat G, Hermelin B. Overexpression of p53 mRNA in Colorectal Cancer and its Relationship to p53 Gene Mutation. British Journal of Cancer. 1997;75(4):528-536.

8. Geutskens SB, Diana JM, Marjolijin M, Hans O, Aart GJ, Rob CH. Characterisation of the p53 Gene in The Rat CC531 Colon Carcinoma. Gene Therapy and Molecular Biology. 2000;5:81-86.
9. Ahnen DJ, Polly F, Gang Q, Cecelia FP, Laura CL, Paul AB, Jr. Grant S, John DW, John SM, Frank LM. Jr. Ki-ras Mutation and p53 Overexpression Predict the Clinical Behavior of Colorectal Cancer: A Southwest Oncology Group Study. Cancer Research. 1998;58:1149-1158.
10. Forslund A, Cristina L, Marianne A, Hans B, Kent L. Mutations and Allelic Loss of p53 in Primary Tumor DNA From Potentially Cured Patients With Colorectal Carcinoma. Journal of Clinical Oncology. 2001;19(11):2829-2836.
11. Sameer AS, Shah ZA, Syeed N, Bandy MZ, Bashir SM, Bhat BA, Sidiqi MA. TP53 Pro47Ser and Arg72Pro Polymorphisms and Colorectal Cancer Predisposition in an Ethnic Kashmiri Population. Genetics and Molecular Research. 2010;9(2):651-660.
12. Snell RS. Anatomi Klinik untuk Mahasiswa Kedokteran edisi 6. Jakarta: Penerbit Buku Kedokteran EGC; 2002.
13. Price SA, Lorraine CW. Patofisiologi Konsep Klinik Proses-proses Penyakit. Edisi 6. Traslater: Adji Dharma. Jakarta: Penerbit Buku Kedokteran EGC; 2006.
14. Anonymous. 2020. [cited 2020 Aug 2]. Available from: http://www.TotalKesehatanAnda.com.
15. Nagorni A. Genetics Of Colorectal Cancer. Facta Universitatis. Series. Medicine and Biology. 2002;9(2):142-149.
16. Pelengaris S, Michael K. The Molecular Biology of Cancer. Australia: Blackwell Publishing; 2006.
17. Rochestry S. Terapi Kanker pada Tingkat Molekular. Cermin Dunia Kedokteran. 2000;127:5-10.
18. Russo A, Manuela M, Ines Z. p53 Mutation in L3-Loop Zinc-binding Domain, DNA-Ploidy, and S Phase Fraction Are Independent Prognostic Indicators in Colorectal Cancer: A Prospective Study with a Five-Year Follow-Up. Cancer Epidemiology, Biomarkers and Prevention. 2006;11:1322-1331.
19. Anonymous. 2020. [cited 2020 Aug 2]. Available from: http://www.ebookpangan.com