ejpmr, 2021,8(3), 223-228

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

A REVIEW ON CHEMOTHERAPY OF COLON CANCER

Imad Ahmad*, Sindhu Gupta, Amresh Gupta, Amit K. Srivastava, Om Prakash Verma, Neelam Verma

Goel Institute of Pharmacy and Sciences, Faizabad Road, Lucknow, Uttar Pradesh – 226028.

***Corresponding Author: Imad Ahmad**
Goel Institute of Pharmacy and Sciences, Faizabad Road, Lucknow, Uttar Pradesh – 226028.
DOI: https://doi.org/10.17605/OSF.IO/DS69W

Article Received on 29/12/2020 **Article Revised on 19/01/2021** **Article Accepted on 09/02/2021**

ABSTRACT

The treatment of cancer began at the 20th century by developing prescript to screening of chemicals using transplantable tumors in rodents. Cancers were treated with one drug on a time. Now a mixture of 2–5 drugs is given in intermittent pulses to realize total tumor cell kill with most common side effects like Hair loss, loose motion, Infections etc. 10% – 15% of early-stage colon cancers harbor either deficient mismatch repair (dMMR), microsatellite instability high (MSI-H) or POLE exonuclease domain mutations, and are characterized by high tumor mutational burden and increased lymphocytic infiltrate. Metastatic dMMR colon cancers are highly sensitive to immune checkpoint inhibition, and recent data show POLE-mutant tumors are similarly responsive. The 'rise' of colorectal cancer in developed countries can be attributed to the increasingly ageing population, unfavorable modern dietary habits and an increase in risk factors such as smoking, low physical exercise and obesity. For these reasons, and the recognition that colorectal cancer is long preceded by a polypoid precursor, screening programs have gained momentum.

KEYWORD: Chemotherapy, colon cancer.

INTRODUCTION

We are live in an era with improved worldwide average living standards and increased access to adequate healthcare that has considerably improved the diagnosis and treatment of diseases. However, although death rates from communicable diseases have improved globally as a result of these medical improvements, cancer-related mortality has increased by almost 40% over the past 40 years. A further 60% increase is expected in the coming 15 years, with 13 million people estimated to die of cancer in 2030.[1] Colorectal cancer was rather rare in 1950, but has become a predominant cancer in Western countries, now accounting for approximately 10% of cancer-related mortality. The incidence is change not only apparent in the rates of sporadic disease, but also in some familial cancer syndromes. Indeed, given that rates of Helicobacter pylori infection (a causative factor of gastric cancer) have fallen dramatically, colorectal cancer is now the predominant presentation of lynch syndrome, whereas carriers of this syndrome used to be predominantly affected by gastric cancer.[2-4] The famous German chemist Paul Ehrlich firstly developing drugs to treat infectious diseases. Ehrlich coined the term "chemotherapy" and defined it as use of chemicals to treat disease and also documented the effectiveness of animal models to screen a series of chemicals for his potential activity against diseases, an accomplishment that had major ramifications for antineoplastic drugs development. Colorectal cancer (CRC) is the third most common cancer, with a worldwide annual incidence of over 1.2 million cases and a mortality rate of approximately 50%.[5-6] Around, 80% of patients with CRC have localized and respectable disease at diagnosis, with 5-year survival varying from 90% in stage I to 70%–80% in stage II and 40%–65% in stage III disease. The risk of recurrence also depends on the pathological stage of the primary tumor (30% in stage II and 50% in stage III) and is higher within the first 2 years after surgery.[7] The treatment of respectable disease is surgery ±adjuvant fluoropyrimidine-based chemotherapy depending on the pathological stage. In 1908, his use of the rabbit model for syphilis led to the event of arsenicals to treat this disease. Paul also anxious about drugs to treat cancer, including aniline dyes and therefore the first primitive alkylating agents, but apparently wasn't optimistic about the prospect for fulfillment. Surgery and radiotherapy dominated the sector of cancer therapy into the 1960s till it became clear that cure rates after ever more radical local treatments had plateaued at about 33% thanks to the presence of heretofore-unappreciated micro-metastases and new data showed that combination chemotherapy could cure patients with various advanced cancers.[8-11] In this review we focused on cancer chemotherapy, which is a type of standard cancer therapy, and on modern biological types of targeted therapy. In early 1970s, bleomycin, vinblastine and cisplatin are novel drugs used in

chemotherapy, however, they induced severe side effects, such as vomiting up to 12 times per day.[12]

Where is colon is located?

Most of the massive intestine rests inside a cavity within the abdomen called the greater peritoneal sac. Parts of the colon are ready to move quite freely within the greater peritoneal sac because the undigested food is passing through it. As the colon heads towards the rectum, it becomes fixed to the tissues behind the greater peritoneal sac, a neighborhood called the retroperitoneum. The end portion of the massive intestine, the part that resides within the retroperitoneum, is that the rectum. Unlike much of the remainder of the colon, the rectum is fixed in situ by the tissues that surround it. Because of its location, treatment for rectal cancer often is different than treatment for cancer of the remainder of the colon.

Cancer Drug Development

The first four decades of the 20th century were primarily dedicated to model development. The major limitations of drug discovery were two-fold: first, the event of models that would effectively be wont to reduce the vast repertoire of chemicals to those few that have activity against cancer in humans, and second, the access to clinical facilities to check such agents. This advance allowed the standardization of model systems and therefore the testing of larger numbers of chemicals. Significant efforts were subsequently focused on identifying the perfect model system for anti-neoplastic testing, which then became a serious thrust of research for subsequent several decades.[13–18] Shear's program was the primary to check a broad array of compounds, including natural products, and had both inter-institutional and international collaborations. He ultimately screened near about 3,000 compounds using the murine S37 as his model system. This failure was partially thanks to the antipathy toward the testing of medicine to treat cancer but also to a scarcity of data and knowledge on the way to test potentially toxic chemicals in humans. The most excitement during this era was generated by the introduction of hormonal therapy when, in 1939, Charles Huggins, supported an early observation on the effect of estrogens on breast cancer made by Beatson in 1896, treated men with prostate cancer with hormones and was able to show responses by decreases in acid phosphatase levels.[19] Although this exciting piece of labor was a crucial addition to the systemic treatment of cancer and earned Huggins a Nobel prize, it had been not considered to be related to the difficulty of whether chemicals could ever control cancer.[20]

Principles of Chemotherapy of Cancer

1. Cancer chemotherapy are analogy is deformed with bacterial Chemotherapy the malignant cell being viewed as an aggressor. However, there are two differences.
   (a) Bacterial metabolism differs markedly from that of the host, while malignant cells are actually host cells with deranged regulation of growth and differentiation and comparatively minor other differences. Therefore, selectivity of drugs is limited. A number of measures which enhance selectivity of medicine for the tumor got to be utilized. However, lately some unique tumor antigens and oncogenes (like the CML-tyrosine protein kinase gene) have been identified, which provide specific targets for drug therapy.
   (b) Microorganisms is infected by the amenable to immunological and other host defense mechanisms. This is absent or minimal against cancer cells.
2. One clonogenic malignant cell is capable of manufacturing progeny which will kill the host. Survival time is said to the amount of cells that escape chemotherapeutic attack.
3. In any type of the cancer, sub populations of cells differ in their rate of proliferation and susceptibility to cytotoxic drugs. These type drugs are kills cancer cells by first order kinetics, i.e., the few fraction of cells present is killed by one treatment.
4. Drug number of cycles of combined chemotherapy which may effectively palliate large tumor burdens could also be curative when applied to minute residual tumor cell population after surgery and/or irradiation. This is the idea of the combined modality approach
5. Whenever, complete remission should be the goal of cancer chemotherapy: drugs are often utilized in maximum tolerated doses. The Intensive regimens used at an early stage in the disease yield better results.
6. Cancers were treated with one drug at a period. Now a mixture of 2–5 drugs is given in intermittent pulses to realize total tumor cell kill, giving time in between for normal cells to recover. However, some tumors are still treated with a single drug.[21]

Common Side Effect Of Chemotherapy[22]

Here are some most common side effects caused by chemotherapy like Fatigue, hair loss, easy bruising and bleeding Infection Anemia (low red blood cell counts). Nausea and vomiting, appetite changes, constipation, diarrhea are common. Tongue, mouth and throat problems like sores and pain with swallowing are also side effects of cancer chemotherapy. Nerve problems, peripheral neuropathy like numbness, tingling, and pain, nail changes and skin changes like dry skin and color change Urine and bladder changes and kidney problems, Weight changes, Mood changes, Changes in libido and sexual function fertility problems are also side effects of this therapy.

Treatment Strategies

Now a day, many strategies are adapted to administered chemotherapeutic drugs. Chemotherapeutic drugs could also be used with a curative purpose or it's going to be aimed to prong life.

a) Combined chemotherapy is that the one sorts of treatment strategy where more one sort of therapy are often adopted at a time to treat cancer, like radiotherapy, surgery and/ or hyperthermia. However, induction chemotherapy is used for the first-time treatment of cancer with anticancer drug.[23]
b) Consolidation chemotherapy is generally given after remission in order to prolong the overall disease-free time and improve overall survival.[24]
c) Intensification chemotherapy is just like consolidation therapy but a special drug than induction therapy is employed.
d) In combined chemotherapy, different dugs are having different sorts of mechanism of action and their side effects. The most advantage of combined chemotherapy is to attenuate the probabilities of development of resistance to anybody the drug. Also the drugs are often administered at lower dose with minimal side effects and toxicity.
e) Neo adjuvant chemotherapy is employed before an area treatment like surgery, and is supposed to shrink the first tumor. It is also used to a condition where a high risk of micro metastatic disease observes.[25]
f) This therapy (Neo adjuvant chemotherapy) can be used where there is a little a chance or evidence of cancer present and also there is risk of recurrence. It is also beneficial to kill the cancerous cells that have proliferated to other part of the body.[26]
g) Maintenance chemotherapy is one where a repeated low-dose is employed to treat for prolong remission.
h) Salvage chemotherapy is beneficial to easily decrease tumor load and increase anticipation.[27-28]

Pathophysiology

The environmental and genetic factors that cause colorectal cancer do so by promoting the acquisition of hallmark behavior of cancer in colon epithelial cells.[29-30] One way these hallmark cancer traits are acquired is through the progressive accumulation of genetic and epigenetic alterations that activate oncogenes and inactivate tumor suppressor genes. The loss of genomic and/or epigenomic stability has been observed in the majority of early neoplastic lesions in the colon (namely, aberrant crypt foci, adenomas and serrated polyps) and is likely a central molecular and pathophysiological event in the initiation and formation of colorectal cancer.[31-32] The loss of genomic and epigenomic stability accelerates the accumulation of mutations and epigenetic alterations in tumor suppressor genes and oncogenes, which drive the malignant transformation of colon cells through rounds of clonal expansion that select for those cells with the most aggressive and malignant behavior.[33-35] In this model, mutations in oncogenes and tumor suppressor genes in these cells lead to the formation of cancer stem cells, which are essential for the initiation and maintenance of a tumor. In the 'classic' colorectal cancer formation model, the vast majority of cancers arise from a polyp beginning with an aberrant crypt, which then evolves into an early adenoma (<1 cm in size, with tubular or tubule villous histology). The adenoma then progresses to an advanced adenoma (>1cm in size, and/or with villous histology) before finally becoming a colorectal cancer. This process is driven by accumulation of mutations and epigenetic alterations and takes 10–15 years to occur but can progress more rapidly in certain settings (for example, in patients with Lynch syndrome).[36] Notably, although the histology of conventional tubular adenomas is fairly homogeneous, the molecular biology of these polyps is heterogeneous, which might explain why some adenomas progress to colorectal cancer.[37-38]

Drug for Colon Cancer

Irinotecan

It is a prodrug which is decarboxylated in liver to the active metabolite SN-38. Irinotecan is cholinergic effects produced in some patients because it inhibits AChE. These effects can be suppressed by prior atropinization. It has been combined with 5-FU and leucovorin. Dose limiting toxicity is diarrhea. Neutropenia, thrombocytopenia, hemorrhage, body ache and weakness are the other adverse effects.

The active metabolite SN-38 is inactivated by glucuronidation within the liver. Individuals expressing the UGT1A1*28 allele of glucuronic transferase enzyme are more susceptible to irinotecan induced diarrhea and neutropenia, because they fail to inactivate SN-38.

Dose: 125 mg/m2 i.e., over 90 min, weekly for 4 weeks.[39]

Risk Factors

Among the risk factors related to developing colorectal cancer, which is estimated that 35% can be explained by hereditary factors. Nevertheless, family history has great relevance for risk of colorectal cancer, as well as colon or rectal cancer, hereditary diseases such as familial Adenomatous polyposis, hereditary colon cancer without polyposis which is known as Lynch syndrome.[40] It is associated with gene mutations implicated in the pathway of repair of bad DNA coupling/ mating (MMR, mismatch repair) specifically MLH1, MSHS2, MSH6, and PMS2. The mutations in MLH1 and MLH2 are majority about 90% of the mutations found in families of hereditary colon cancer with or without polyposis. However, APC germinal online mutations, repair MTHYU, SMAD4, BMPR (Alq3), STK11, represent less than 5% of all cases of colorectal cancer.[41] It is estimated that these genetic syndromes represent about 10% of all cases of colorectal cancer; however, about 25% of cases the familial history contributes to an increased risk of developing colorectal cancer in the absence of these genetic syndromes.[42] Factors such as history of ulcerous colitis, Chron's disease, personal history of polyposis, colon, rectal, ovarian, endometrium, breast cancer, and diabetes mellitus are related to a 30-50% greater risk of developing colorectal cancer, and

about 75% of the malignant tumors of the colon and rectum are presented without related any of these risk factors, the relationship between hyperplastic polyposis and cancer is controversial. Adenomatous polyps are common in adults which are over 50 years old, but most polyps will not turn malignant. Its histology and size determine its clinical relevance. Risk factors for malignancy in hyperplastic polyps include polyp size equal to or above 10mm, or dysplasia, right colon localization. A focus of an adenoma within the polyp (mixed polyp hyperplastic-adenomatous); in which the presence of more than 20 hyperplastic polyps in the colon, and familial history of colon cancer. In a period of a clear evolution between 10-15 years with define stages, initiating as a minor dysplasia that progresses depending on the genetic modifications to moderate or severe. The dissemination pathways is determined by either hematic or lymphatic, which defines the speed of growth and the time of evolution of the disease, however there have been reported cases of implantation by surgical manipulation after a laparoscopic colectomy.[43] The adenomatous polyps are common in adults over 50, but most of the polyps will not turn malignant. The histology and size will determine its clinical relevance. The risk factors for a hyperplastic polyp to turn malignant includes size equal to or above to 10mm, dysplasia, location in the right colon, a focus of adenoma inside another polyp (mixed hyperplastic-adenomatous polyp), presence of more than 20 hyperplastic polyps in the colon, and familial history. It develops with a clear evolution between 10-15 years starting as mild dysplasia that progresses depending on the genetic modifications to moderate or severe. The dissemination pathways are either hematic or lymphatic, and defines the growing rate and the time of progression of the disease; however cases have been reported of surgical implantation following a laparoscopic colectomy. The adenomatous polyps are common in adults over 50, but most of the polyps will not turn malignant. The histology and size will determine its clinical relevance. The risk factors for a hyperplastic polyp to turn malignant includes size equal to or above to 10mm, dysplasia, location in the right colon, a focus of adenoma inside another polyp (mixed hyperplastic-adenomatous polyp), presence of more than 20 hyperplastic polyps in the colon, and familial history. It develops with a clear evolution between 10-15 years starting as mild dysplasia that progresses depending on the genetic modifications to moderate or severe. The dissemination pathways are either hematic or lymphatic, and defines the growing rate and the time of progression of the disease; however, cases have been reported of surgical implantation following a laparoscopic colectomy.[44]

Protecting Factors

The ingestion of non-steroidal anti-inflammatory drugs reduce the risk of colorectal cancer, however the molecular basis has demonstrated, which regulates the overexpression of the receptor of the epidermal growth Factor (EGFR), which is overexpressed in the 80% of the cases colorectal cancer, as an early event in colorectal tumorigenesis. The overexpression of the cyclooxygenase 2 (COX-2) triggers the activation of the transcription factor of the c-Jun dependent protein activator 1 (AP-1) that binds to the promoter of EGFR; therefore, selective COX-2 inhibitors can be used as quimio preventive activity against colorectal cancer. The variety in consumption was not associated with a decrease in the risk of colon cancer, but if there is an increased with a high in the variety in fruit consumption reflected in a 41% of higher risk for those who ingest more than 8 different fruits every two weeks.[45]

CONCLUSION

There are numerous sorts of treatments that this is often not an exhaustive listing of all the chemotherapy strategies available to oncologists. Further improvements of this treatment strategy will undoubtedly involve the event of more efficient anticancer drugs. Although it's hoped that tumor organic phenomenon profiles can help us select appropriate patients for specific treatments, development of drug resistance to chemotherapy or biologic therapy remains a serious limitation. To end, more ongoing and future trials are investigating new effective combinations consisting not only of chemotherapy but also of biologic agents designed to focus on identified cell-signaling pathway are active in settings of disease progression. These advances in therapy will still help us overcome tumor resistance and disease progression in any given patient with carcinoma.

REFERENCES

1. Kuiper's EJ, Rosch T, Bretthauer M. Colorectal cancer screening--optimizing current strategies and new directions. Nat Rev Clin Oncol, 2013; 10: 130–42. Review of current state of art of colorectal cancer screening.
2. Warthin AS. Heredity with reference to carcinoma: as shown by the study of the cases examined in the pathological laboratory of the University of Michigan. Arch Intern Med, 1913; 12: 546–55.
3. Chapelle LG, et al. Risk and epidemiological time trends of gastric cancer in Lynch syndrome carriers in the Netherlands. Gastroenterology, 2010; 138: 487–92.
4. Vasen HFA, Tomlinson I, Castells A. Clinical management of hereditary colorectal cancer syndromes. Nat Rev Gastroenterol Hepatol, 2015; 12: 88–97.
5. Cunningham D, Atkin W, Lenz H-J, et al. Colorectal cancer. The Lancet, 2010; 375: 1030–47.
6. Brenner H, Kloor M, Pox CP. Colorectal cancer. The Lancet, 2014; 383: 1490–502.
7. Sargent D, Sobrero A, Rothay A, et al. Evidence for cure by adjuvant therapy in colon cancer: observations based on individual patient data from 20,898 patients on 18 randomized trials. J Clin Oncol, 2009; 27: 872–7.

8. Breasted JH. The Edwin Smith surgical papyrus, Translated for The New York Historical Society. Chicago (IL): University of Chicago Press, 1930.
9. Papac RJ. Origins of cancer therapy. Yale J Biol Med, 2001; 74: 391-8.
10. De Vita VT. The evolution of therapeutic research in cancer. N England J Med, 1978; 298: 907-10.
11. Osler W. The principles and practice of medicine, New York: D. Appleton and Company, 1893; 708.
12. Koeppen BM, Stanton BA, editors. Berne and Levy Physiology. 7th edition. Elsevier; Amsterdam, 2018; 880.
13. Goldin A, Schepartz SA, Venditte JM, DaVita VT. Historical development and current strategy of the National Cancer Institute Drug Development Program. In: Busch H, DeVita VT, editors. Methods in cancer research, V16 (A). New York: Academic Press, 1979; 165–245.
14. Hirschberg E. Patterns of response of animal tumors to anticancer agents. Cancer Res., 1963; 23: 521–980.
15. Shear MJ, Hartwell JL, Peters VB, et al. Some aspects of a joint institutional research program on chemotherapy of cancer: current laboratory and clinical experiments with bacterial polysaccharide and with synthetic organic compounds. In: Moulton FR, editor. Approaches to tumor chemotherapy. Washington (DC): American Association for the Advancement of Science, 1947; 236–84.
16. Zubrod CG, Schepartz S, Leiter J, Endicott JM, Carrese LM, Baker CG. The chemotherapy program of the National Cancer Institute: History, analysis, and plans. Cancer Chemother. Rep, 1966; 50: 349–540.
17. Zubrod CG, Schepartz SA, Carter SK. Historical background for the National Cancer Institute's drug development thrust. Natl Cancer Inst Monograph, 1977; 45: 7–11.
18. Boy land E. Experiments on the chemotherapy of cancer. I. The effects of certain antibacterial substances and related compounds. Biochemistry J, 1938; 32: 1207–13.
19. Yoshida T. The Yoshida sarcoma, an ascites tumor. Gann, 1949; 40: 1–20.
20. Beatson GT. On the treatment of inoperable cases of carcinoma of the mamma: suggestions for a new method of treatment, with illustrative cases. Lancet, 1896; 2: 104–7; 162–165.
21. Huggins C, Hodges CV. Studies on prostatic cancer. I. The effects of castration, of estrogen and of androgen injection on serum phosphatase in metastatic carcinoma of the prostate. Cancer Res., 1941; 1: 293–7.
22. https://www.cancer.org/treatment/treatments-and-side-effects/treatment types/chemotherapy /chemotherapy-side-effects.html.
23. Adam R, Pascal G, Casting D, Azulay D, Delvart V, et al. Tumor progression while on chemotherapy: a contraindication to liver resection for multiple colorectal metastases. Ann Surg., 2004; 240(6): 1052- 1061.
24. Einhorn LH, Crawford J, Birch R, Omura G, Johnson DH, et al. Cisplatin plus etoposide consolidation following cyclophosphamide, doxorubicin, and vincristine in limited small-cell lung cancer. J Clin Oncol, 1988; 6(3): 451-456.
25. Buzdar AU, Singletary SE, Theriault RL, Boozer DJ, Valero V, et al. Prospective evaluation of paclitaxel versus combination chemotherapy with fluorouracil, doxorubicin, and cyclophosphamide as neoadjuvant therapy in patients with operable breast cancer. J Clin Oncol, 1999; 17(11): 3412-3417.
26. Peters III WA, Liu PY, Barrett RJ, Stock RJ, Monk BJ, et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. J Clin Oncol, 2000; 18(8): 1606-1613.
27. Fishman PN, Pond GR, Moore MJ, Oza A, Burkes RL, et al. Natural history and chemotherapy effectiveness for advanced adenocarcinoma of the small bowel: a retrospective review of 113 cases. American J Clin Oncol, 2006; 29(3): 225-231.
28. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell, 2000; 100: 5770.
29. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell, 2011; 144: 646–74.
30. Colossi D, Brandi G, Bazzoli F, Ricciardi Ello L. Molecular pathways involved in colorectal cancer: implications for disease behavior and prevention. Int J Mol Sci., 2013; 14: 16365–85.
31. Grady WM, Carethers JM. Genomic and epigenetic instability in colorectal cancer pathogenesis. Gastroenterologym,2008; 135: 1079–99.
32. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell, 1990; 61: 759–67.
33. Lengauer C, Kinzler KW, Vogelstein B. Genetic instabilities in human cancers. Nature, 1998; 396: 643–9.
34. Kinzler KW, Vogelstein B. Lessons from hereditary colorectal cancer. Cell, 1996; 87: 159–70.
35. Zeki SS, Graham TA, Wright NA. Stem cells and their implications for colorectal cancer. Nat Rev Gastroenterol Hepatol, 2011; 8: 90–100.
36. Jones S, et al. Comparative lesion sequencing provides insights into tumor evolution. Proc Natl Accad Sci., 2008; 105: 4283–4288.
37. Luo Y, et al. Differences in DNA methylation signatures reveal multiple pathways of progression from adenoma to colorectal cancer. Gastroenterology, 2014; 147: 418–29. e8.
38. Van England M, Derks S, Smits KM, Meijer GA, Herman JG. Colorectal Cancer Epigenetics: Complex Simplicity. J Clin Oncol, 2011; 29: 1382–1391.
39. Tripathi, K. D. Essentials of Medical Pharmacology, 7th edition, New Delhi, India: Jaypee Brothers Medical publishers (P) LTD, 2018; 857-878.

40. Gala M, Chung DC. Hereditary colon cancer syndromes. Seminars in Oncology, 2011; 38: 490-9.
41. Altona L, Johns L, Järvinen H, Macklin J, Houston R. Explaining the familial colorectal cancer risk associated with mismatch repair (MMR)-deficient and MMR-stable tumors. Clin Cancer Res., 2007; 13: 356-61.
42. Zhang K, Civan J, Mukherjee S, Patel F, Yang H. Genetic variations in colorectal cancer risk and clinical outcome. World J Gastroenterol, 2014; 20: 4167-77.
43. Li H, Zhu F, Boardman LA, Wang L, Oi N, Lui K, et al. Aspirin Prevents Colorectal Cancer by Normalizing EGFR Expression. Biomedicine, 2005; 2(5): 447-55.
44. Sánchez AR, Martín FM, Palma MS, López PB, Bermejo LM, Gómez CC. Fiber-type indication among different pathologies. Nutra. Hosp, 2015; 31(6): 237-83.
45. Lenders M, Siersma PD, Overread K, Tjonneland A, Olsen A, Boutron-Ruault MC, et al. Subtypes of fruit and vegetables, variety in consumption and risk of colon and rectal cancer in the European Prospective Investigation into Cancer and Nutrition. Int J Cancer, 2015; 137(11): 2705-14.