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Case Review

An Innovative Combination of Drugs Improves the Treatment of Colorectal Cancer. Situation in Argentina

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A combination of drugs directed against a genetic alteration has increased the survival of patients with colorectal tumors in an international study presented at the International Congress of Gastrointestinal Cancer held this week in Barcelona, Spain.

The drugs attack the genetic alteration BRAF V600E, which is present in 15% of colorectal tumors.

Patients with this mutation, who usually have a poor prognosis, are those who will benefit from the treatment.

In Argentina, according to data from the International Agency for Research on Cancer, a body dependent on the World Health Organization, colon-rectum cancer is the second highest incidence in Argentina, both in men and women: in 2018 were diagnosed 15,692 cases.

In women, these tumors represent 10.8% of the total, behind breast cancer (32.6%). In men, 14.5%, behind prostate cancer (19.7%). Regarding mortality, also in 2018, 3,970 women and 4,751 men died from these tumors, which also place them second in mortality (behind breast cancer in women and lung cancer in men). 12.8% of total cancer deaths last year were due to these tumors.

However, if detected early, the chances of cure are over 90%, according to the National Health Secretariat. Colorectal cancer develops in the colon and rectum (large intestine), and in more than 80% of cases a polyp called adenoma is first generated, which can grow slowly for more than 10 years and turn into cancer if it is not removed.

Colon and rectal cancer begins with a polyp. That is why it is essential to carry out periodic checks to diagnose these polyps. The main screening tool is colonoscopy, a study that uses a flexible tube with a camera to thoroughly examine the colon and rectum. It can also be diagnosed with a fecal occult blood test, since polyps or tumors can cause the appearance of blood in the stool.

From the Ministry of Health recommend that all people aged 50 to 75 years even if they have no symptoms to perform periodic check-ups. If you have a family history, previously had polyps or suffer from ulcerative colitis or Crohn's disease, the controls should start earlier. The doctor should also be consulted for symptoms such as bleeding or changes in the usual way of bowel evacuation, frequent abdominal or rectal pain, anemia or weight loss.

The Argentine Society of Gastroenterology (SAGE) made a special call and among the main topics of discussion is a new therapeutic approach that grows in the world: specialists begin to advise patients to begin preventive studies against colorectal cancer at 45 years. That is, five years before what until recently was the indication of rigor.

This new perspective arises from a recent report of the American Cancer Society, which ensures that in the last decade, in the United States, cancer cases increased just in that age range: people between 45 and 50 years. Because of this, they suggest starting studies before the age of 50.

The information arrived from the USA puts the doctors on alert.

First, start to see what happens in Argentina and see if we also have an increase in incidence. And, based on the findings we find, generate consensus to see if it is also feasible to lower the age of the beginning of the prevention study.

A diet very high in red and smoked meats increases the chances of developing the disease, according to specialists.

In the world, every year, 80 thousand people die from this cancer and there are more than one million new cases. Locally, some 7 thousand people die due to this disease and there are more than 13 thousand new cases every year.

In Argentina our campaign has to do with generating awareness. Colon cancer remains a health problem of the first order. Nearly 20 people die every day in Argentina from colon cancer.

The preventive studies

- Just as this cancer is frequent and deadly, it is also one of the most easily preventable. For a tumor to form, before, in the same intestine, in the internal part, a lesion is formed that is benign, called adenomatous polyp.
- It takes 10 to 15 years to gro w and become cancer. It gives us a window of time to do studies to the population, find them, resect them and thus prevent the appearance of cancer.
- As it appears with greater frequency between 65 and 70 years, until now the recommendation was for patients to take preventive studies (be it colonoscopy or fecal occult blood test) from the age of 50.
- They have to do both men and women, healthy and without symptoms. The colonoscopy, once every ten years, if it is normal, and the analysis of the bleeding hidden in fecal matter once a year.
- But in Argentina there is still no awareness of this.
- Only 27% of the population of that age or more had colon cancer prevention studies in the year. We must get all of them to do the study.
- Patients who have family members with this type of cancer should start the preventive studies much earlier: between 35 and 40.
- The older the risk of developing this cancer increases.
- The low consumption of fibers or folates, a diet very high in red and smoked meats, obesity and diabetes increase the chances of suffering from the disease.

Advanced disease

- Metastatic colon cancer: 8 out of 10 are disseminated before diagnosis.
- A group of researchers from the Stanford University School of Medicine (USA) demonstrated in a study of 3,000 patients that up to 8 out of 10 cases of metastatic colon cancer-that is, cancer cells migrate to other parts of the body. body- they are disseminated before their diagnosis.
- Although detected early the chances of cure are over 90%, colon cancer or colorectal cancer is the second leading cause of death in men and women in the United States
- Metastases mainly affect the liver and rarely reach the brain. The genomic changes that cause this cancer are called 'driver mutations'.

In this sense, Christina Curtis, professor of medicine and genetics at Stanford and author of the study, tried to reconstruct the process of metastasis in different patients by analyzing the tumor genome data, with the aim of identifying the drivers.

For the development of this study, published in Nature Genetics, the researchers compared genetic mutations in the primary tumors of 23 participants with the patterns of their liver or brain metastases to look for similarities or differences between primary and metastatic cancers obtained in the same person.

Then these data were used to create an evolutionary cancer pattern for each patient. Thus, they were able to observe that in 17 of 21 patients the metastatic tumors were initiated by a cell, or a small group of similar cells, that separated from the primary tumor at the beginning of its development.

The cells that formed the metastasis were more closely related to the ancestors of the primary tumor than their current relatives and the metastasis shared the majority of the first drivers present in the scheme, presenting few additions, suggesting that these cancers have acquired a metastatic competence very early during its growth.

To further determine when the metastasis occurred, the team developed a computer program and a statistical method to measure the metastatic propagation time in relation to the size of the

primary tumor in an individual patient. In this way, they were able to observe a similar pattern in most of the cases evaluated. Thus, they applied these theories to 938 people with metastases and 1,813 with non-metastatic cancer.

In this regard, Curtis noted that mutations of the PTPRT gene were found in most cases with metastatic cancer. Previous studies have shown that the loss of function of this gene increases the activity of the STAT3 protein, which improves cell survival. Thus, the researchers speculated that the inhibition of STAT3 can frustrate tumor growth and metastasis.

These data indicate that metastasis may occur early in human colorectal cancer and highlights the need for early diagnosis of aggressive diseases. New biomarkers based on specific combinations of alterations could allow the identification of lethal colorectal tumors at an early stage so that they can be intercepted and treated appropriately.

An innovative combination of drugs

- Attempts so far to neutralize the BRAF V600E mutation with a single drug had been disappointing because the tumor cells quickly became resistant to treatment.
- To address this problem, a strategy similar to that used against the AIDS virus has been applied, combining antiretroviral drugs to prevent the onset of resistance.
- According to the first results of the Beacon study, this strategy has increased the median survival of patients with the mutation by 67%. Some of the participants, who had a short life expectancy when they enrolled in the study, survive more than a year and a half after starting treatment.

Targeted therapies

The drugs evaluated are part of the so-called targeted therapies (or molecular therapies). They point directly to tumor cells and are different from chemotherapies, which non-selectively attack all dividing cells.

The study involved 665 patients from some twenty countries. Approximately one third received a combination of three drugs that attack three different molecules altered by the BRAF V600E mutation. Another third received a combination of two drugs. The remaining third received conventional treatment, which consists of combining a chemotherapy with a drug against BRAF V600E.

Although the study has not yet finished, the first results have already shown that combinations of two and three drugs are better than conventional treatment.

The conclusion is so clear that patients undergoing chemotherapy within the study have been offered the possibility of changing their treatment by a combination of targeted therapies.

However, there is not enough data yet to know if the combination of two drugs (cetuximab and encorafenib) or the combination of three (the same ones plus binimetinib) is better.

As is usual in trials of new oncological therapies, the study has been limited to patients for whom there were no better treatment options.

They were patients who had already been treated after developing metastases and in whom the cancer was still progressing.

Once the efficacy of the combination of drugs in this group has been proven, the researchers intend to test the therapy in not-so-advanced phases of the disease, in which they hope to obtain equally positive results.

In my opinion, for the first time we have a treatment directed against a genomic alteration that makes colorectal cancer progress and I think it is possibly the most important advance against this type of tumor since the appearance of antibodies against the EGFR receptor fifteen years ago. In the future, the presence of the BRAF V600E mutation will have to be systematically checked in patients with colorectal cancer to decide the best treatment for each case.

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