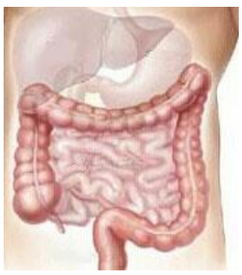
COLORECTAL CANCER RESEARCH UPDATES

Month Ending July 13th, 2017



The following colorectal cancer research update extends from May 18th to July 13th, 2017 inclusive and is intended for informational purposes only.

CONTENT

DRUGS / SYSTEMIC THERAPIES

1. Addressing BRAF mutations in colon cancer: new data from ASCO 2017 (Jun 09/17)

BRAF and BRAF V600E mutations may be associated with very poor prognosis in colon cancer. A recent analysis examined patients with BRAF V600E-mutant tumours compared to BRAF wild-type tumours, revealing a median survival of 11 months compared to 40+ months, respectively. As such, researchers are using BRAF as a strong prognostic indicator for the disease. While BRAF inhibitors have been successful in the treatment of other cancers such as melanoma, the same success has not been observed in colon cancer. Since 50% of patients with melanoma have the same BRAF V600E mutation, single agent BRAF inhibitors such as vemurafenib have led to 80% response rates. The same BRAF inhibitor had a 5% or less response rate in colon cancer, suggesting a different molecular biology behind the disease. Indeed, BRAF V600E mutant colon cancers only make up 8-10% of patients with stage IV disease. A study by the SWOG Cooperative group found that when BRAF inhibitors are used to treat patients with colon cancer, a feedback loop is activated to turn on the epithelial growth factor receptor (EGF receptor), which enables proliferation of cancerous epithelial cells in the colon to continue. Thus, the combination of a BRAF inhibitor such as vemurafenib with an EGF receptor antibody achieved a far more dramatic progression-free survival.

http://www.practiceupdate.com/c/4f967cde-23ff-4dda-b065-c2c3026785c1?elsca1=soc_share-this-email&elsca2=social&elsca3=email

2. ASCO 2017: The IDEA Collaboration: Global study sets new risk-based standard to personalize chemotherapy for colon cancer after surgery (Jun 4/17)

Among patients with stage III colorectal cancer, a recent study found that some patients may only need half of the current standard course of chemotherapy. The analysis surveyed over 12,800 patients enrolled in 6 clinical trials and found that 3 months of chemotherapy was nearly as effective as 6 months in patients with relatively lower recurrence risk. The reduced course of chemotherapy resulted in fewer side effects, including nerve damage which affects patients more severely and persistently the longer the chemotherapy is administered. After a patient undergoes surgery for colorectal cancer, chemotherapy is the current standard adjuvant treatment to lower the chance of cancer recurrence. The current standard includes a combination of chemotherapies: FOLFOX (leucovorin, fluorouracil, oxaliplatin) or CAPOX (capecitabine/oxaliplatin) administered over a period of 6 months. The study found that a shorter, 3-month course of chemotherapy was accompanied by a less than 1% lower chance of being free of colon cancer at 3 years compared to the standard 6-month course. Among patients with a low-risk of cancer recurrence, the difference between a 3-month and a 6-month chemotherapy treatment was even smaller. The study's findings are important as they could apply to around 400,000 colon cancer patients around the world each year who are at lower risk for cancer recurrence. For patients with higher-risk colon cancer, the benefits of a shorter chemotherapy course are not clear and options should be discussed with their doctor to take into account their preference, age and ability to tolerate chemotherapy. Nerve damage was significantly less prevalent in patients who received a 3-month course of chemotherapy compared to a 6-month course (15% vs 45% with FOLFOX and 17% vs 48% with CAPOX).

http://www.ascopost.com/News/55708

3. Effect of post-diagnosis Aspirin and other NSAIDS on survival in colorectal cancer (Jun 22/17)

A study published in the Journal of Clinical Oncology found that long-term survivors of colorectal cancer (CRC) with KRAS wild-type tumours had improved survival with regular use of nonsteroidal anti-inflammatory drug (NSAID) after their diagnosis. Using data from over 2000 patients between the ages of 18 and 74, detailed questionnaires were completed at diagnosis and at 5 years. Regular use of NSAIDS was defined as a minimum use of twice a week for more than one month. After a median follow-up of 10.8 years, 381 patients died, 100 of which died from CRC. Post-diagnostic aspirin-only users had improved overall survival compared to nonusers. The link between post-diagnosis use of any NSAID and overall survival differed significantly according to KRAS mutation status. It was found that overall survival improved with use of any NSAID among participants with KRAS wild-type tumours but not among those with KRAS-mutant tumours. Thus, it was found that among long-term CRC survivors, regular use of NSAIDS post-diagnosis was significantly associated with improved survival in individuals with KRAS wild-type tumours.

http://www.ascopost.com/News/57767

4. FDA approves panitumumab for use in wild-type RAS metastatic colorectal cancer (Jun 30/17)

The US Food and Drug Administration (FDA) has recently approved the use of panitumumab (Vectibix) for use in patients with wild-type RAS metastatic colorectal cancer (mCRC) as a first-line therapy in combination with FOLFOX and as monotherapy following prior chemotherapy. Panitumumab is the first and only human anti-epidermal growth factor receptor (EGFR) antibody approved by the FDA. The FDA also approved the first multigene, next-generation sequencing-based test used to identify the RAS mutation status of a patient's tumour. This sequencing technique a new diagnostics test that enables mCRC treatment to be more streamlined to the patient's unique disease. RAS mutation status provides valuable information regarding

what the first-line treatment option in mCRC could be. So far, panitumumab has shown a significant overall survival benefit among patients whose mCRC does not have RAS mutations. The approval of panitumumab for use among patients with wild-type RAS mCRC was based on the results from the phase III trials PRIME and ASPECCT. The most common adverse reactions of panitumumab as monotherapy are skin rash, fatigue, paronychia (infection of the skin around the fingernails or toenails), nausea, and diarrhea. The most common side effects with panitumumab plus FOLFOX are diarrhea, stomatitis, mucosal inflammation, asthenia (weakness or lack of energy), paronychia, anorexia, hypomagnesemia (lowered magnesium levels in the blood), rash, dermatitis, and dry skin. Researchers emphasize the significance of biomarker testing as a diagnostic tool to aid in the planning of treatment among mCRC patients.

http://www.ascopost.com/News/57801

5. First line cetuximab vs bevacizumab plus chemotherapy in KRAS wild-type advanced colorectal cancer (Jun 30/17)

A phase III trial has demonstrated no overall survival difference with cetuximab vs bevacizumab plus chemotherapy among patients with advanced or metastatic KRAS wild-type colorectal cancer. Over 1000 patients enrolled at National Clinical Trials Network sites in the US and Canada over a 7-year period chose to receive mFOLFOX6 (leucovorin. Fluorouracil, and oxaliplatin) or FOLFIRI (Leucovorin, fluorouracil, and irinotecan) and were randomized to receive either cetuximab or bevacizumab. Of the patients, 97% had metastatic colorectal cancer. The median overall survival was 30.0 months in the cetuximab group vs. 29.0 months in the bevacizumab group. Median progression-free survival was 10.5 months vs 10.6 months. Researchers concluded that no significant difference between the addition of cetuximab vs bevacizumab to chemotherapy as initial biologic treatment could be found among patients with KRAS wild-type untreated advanced or metastatic disease.

http://www.ascopost.com/News/57795

6. New cancer drug makes commonly prescribed chemo drug more effective when given together (Jun 12/17)

The widely-used drug, doxorubicin, is an effective treatment for various kinds of cancer, specifically breast and lung cancers. It is also more cost effective compared to other cancer drugs. It can be toxic to the heart, however, when higher doses are administered as required in the treatment of colon cancer. In a recent study, researchers have demonstrated that combining doxorubicin with a newly-developed drug made it less toxic to the heart, and thus better suited in the treatment of colon cancer. The researchers have previously demonstrated that exposure to cancer-causing agents like pollutants trigger oxidative stress, which in turn contributes to the growth of cancer tissue. Oxidative stress is also implicated in the development of new blood vessels that tumours need in order to proliferate. In the study, researchers show that oxidative signals can be blocked by aldose reductase (AR) inhibitors, specifically the FDA-approved fidarestat. The researchers hypothesized that if these oxidative signals can be blocked, the growth of new blood vessels and thus tumour growth and metastasis can be slowed down or prevented. In the study, it was shown that the growth of cancer cells was prevented using a combination of both drugs in a petri dish as well as in mouse models. The researchers hope that a combination of fidarestat and doxorubicin can be developed to combat different forms of cancer, with the hope that the combined therapy will need less doxorubicin and thus reducing the potential for toxicity.

https://www.sciencedaily.com/releases/2017/06/170612170917.htm

7. Clinical trial: Durvalumab and Tremelimumab and best supportive care vs. best supportive care alone in patients with advanced colorectal adenocarcinoma refractory to standard therapies (June 13/17)

An ongoing clinical trial by the Canadian Cancer Trials Group in collaboration with AstraZeneca aims to examine the outcomes of two drugs in combination with best supportive care (BSC) vs. BSC alone for the treatment of patients with advanced colorectal cancer that is unresponsive to standard therapies.

Durvalumab is a new drug that can be used in the treatment for many types of cancer. It works by allowing the immune system to detect cancer and reactive the immune response to kill cancer cells and reduce the progression of the disease. In animal tests, the drug has been shown to minimize the size of tumours and thus far has been studied in a few individuals but remains unclear whether it can offer better results than standard treatment alone.

Tremelimumab is a new drug that can also be used in the treatment for many types of cancer. It works in a similar way to Durvalumab by boosting the body's immune response to the cancer. In animal models, Tremelimumab has been shown to shrink tumours and has also been studied in a few individuals though its benefits over standard treatment remain unclear. The combination of the two drugs have also been studied and together have been shown to increase tumour shrinkage in animals compared to either drug alone.

Individuals eligible for the study must be 18 years or older. The study accepts both males and females with histologically or pathologically confirmed advanced (metastatic or locally advanced) colorectal cancer that does not qualify for surgery. Participants must have disease that is resistant to other standard treatments, including irinotecan-containing and oxaliplatin-containing regimens.

Please note: the study is no longer enrolling patients.

https://clinicaltrials.gov/ct2/show/NCT02870920

8. Underused blood test could improve treatment for large swath of patients with colon cancer (Jun 29/17)

An analysis of data from over 40,000 patients gathered by the National Cancer Database aimed to examine the benefits of a blood test that measures the presence of the carcinoembryonic antigen (CEA) protein in stage II colon cancer. CEA is a protein that is used as a marker for certain cancers, especially colon cancer. The researchers indicate that these blood test results may help to better classify the cancer and choose the most appropriate course of therapy. In the study, the blood test results could have changed the classification for 17% of stage II colon cancer patients from average risk to high risk, a change that could have resulted in different treatment options such as the decision to include chemotherapy or not. According to senior author of the study, the decision to administer chemotherapy post-surgery is a major decision whose risks and benefits must be carefully taken into consideration. Despite being available for decades, the CEA blood test is not widely used across the country. Indeed, if such a blood test is conducted it is often done after surgery to monitor the cancer's development. The researchers suggest that earlier consideration of the protein level may be advantageous. The study demonstrated that among stage II patients who had surgery but not chemotherapy, the 5-year survival rate was 66% for those with elevated protein levels and 76% for those without elevated levels. For those with elevated protein levels, those who underwent chemotherapy and surgery fared better than those who only had surgery. The study's results support the use of the CEA blood test as a diagnostic tool to determine whether patients with stage II colon cancer should consider chemotherapy in addition to surgery.

http://www.ascopost.com/News/57790

RADIATION THERAPIES

9. ESMO World GI 2017: Right-sided colorectal tumours: an internal radiation advantage (Jul 5/17)

Among patients with colorectal cancer (CRC) with liver metastases, a primary left-sided tumour compared to a right-sided tumour is known to present a significant advantage with respect to treatment response. A recent study, however, has investigated the impact of a combination of first-line chemotherapy and selective internal radiation therapy (SIRT) on patients with a primary right-sided tumour and found that they had a 36% better survival rate compared to chemotherapy alone. Until now, no treatment besides the addition of bevacizumab (Avastin) to chemotherapy has shown improvements among patients with liver metastases originating from right-sided primary tumours. The study followed 739 patients with liver-only or liver-dominant metastatic CRC who were randomized to receive either a modified standard chemotherapy (FOLFOX6, leucovorin, fluorouracil, oxaliplatin plus bevacizumab) alone or combined with SIRT. 24% of patients had their primary tumour originating from the right side of the colon, and 73% from the left. The remaining 3% had primary tumours located on both sides, or unknown. Overall, when taking into account all types of tumours regardless of origin, no difference was observed between the chemotherapy-alone and chemotherapy-plus-SIRT groups with respect to median overall survival and progression-free survival. When the primary tumours were investigated according to origin, however, a clear difference in overall survival was observed when SIRT was added to the chemotherapy regimen among patients with right-sided primary tumours. No such difference was found for patients with left-sided primary tumours. The results are promising as they open a new treatment option for patients who previously were left with few options. Researchers add that there were no differences in side effects between patients with right-sided and left-sided primary tumours, and although patients who underwent both SIRT and chemotherapy experienced more adverse effects compared to patients who underwent chemotherapy alone, they were predictable and manageable. Nonetheless, further research is necessary to better understand why right-sided tumours are more sensitive to this type of radiotherapy, including the molecular factors that are responsible for these outcomes.

http://www.ascopost.com/News/57803

NUTRITION/ HEALTHY LIFESTYLE

Image from: scrolltoday.com

10. Healthy lifestyle after colon cancer diagnosis extends survival (May 18/17)

The results from a 7-year clinical trial examining patients with stage III colon cancer found that patients who reported a healthy lifestyle during and after adjuvant treatment experienced a 42% lower mortality rate and were less likely to have their cancer recur compared to patients who followed less healthy lifestyles. With over a million colorectal cancer survivors in the US alone, the importance of survivorship care and healthy lifestyle guidance is essential in lowering their risk of cancer recurrence. In the study, the effect of two types of adjuvant chemotherapy for colon cancer on cancer recurrence and death was assessed. Lifestyle factors were analysed twice throughout the trial. Over a median follow-up of 7 years, the 91 survivors who scored the highest with respect to healthy lifestyle scores were at a 42% lower risk of death and tended to have a reduced risk of recurrence compared to the 262 survivors with the lowest healthy lifestyle scores. It was observed that associations were driven by no one single lifestyle factor; all factors, such as weight, regular physical activity and a healthy diet were each weighed important. The researchers indicated that since many cancer survivors suffer chronic health problems such as diabetes or heart disease, a healthy lifestyle can certainly help improve overall health alongside colon cancer-specific outcomes in the long run. Results from this study are a clear indication that a healthy lifestyle in addition to standard cancer treatment can make a big difference in reducing mortality associated with colorectal cancer.

http://www.practiceupdate.com/c/e611159b-4a03-44e3-92b6-6b8dc5656fd8?elsca1=soc_share-this-email&elsca2=social&elsca3=email

11. ASCO: nut consumption ups survival in stage III colon cancer (May 19/17)

Two recent studies suggest that eating nuts within an overall healthy diet with regular physical activity can improve colorectal cancer patients' survival. The first study assessed the eating habits of 826 patients with stage III colon cancer. All patients filled out diet questionnaires, including questions about their nut consumption. These patients were followed for about 7 years after their chemotherapy. About 20% of patients indicated that they consumed at least 2 ounces of nuts (does not include peanuts and peanut butter, which are from the legume family) a week – these patients were found to have both a lower risk of cancer recurrence and a higher overall survival. The second study also assessed the lifestyles of patients with stage III colon cancer after chemotherapy. Researchers scored the patients based on their lifestyles by comparing them to the recommendations in the American Cancer Society's Nutrition and Physical Activity Guidelines for Cancer Survivors. The patients were followed up for a minimum of 7 years. It was found that patients who followed the guidelines closely with respect to exercise, diet, and excess weight experienced a 42% lower mortality risk than those who did not. When alcohol consumption was included in the analysis, it was found that the benefit to patients who strictly followed the guidelines was a 51% lower mortality risk and a 36% lower risk of their cancer coming back.

http://www.practiceupdate.com/c/76088f9b-30cc-4ad0-bb51-ee63a24ebced?elsca1=soc_share-this-email&elsca2=social&elsca3=email

http://www.ascopost.com/issues/june-10-2017/tree-nut-consumption-may-improve-outcomes-in-stage-iii-colon-cancer/

Image courtesy of besanworld.com

12. Strengthening the body to prevent colon cancer from returning (Jun 27/17)

The results of a 30-year study in the US demonstrated that nurses who exercised were less likely to develop colon cancer. Furthermore, it was found that among those that did develop colon cancer, those that did exercise were less likely to have their cancer come back. In 2009, the Challenge Trial commenced, including patients from Canada, the US, the UK, Australia, Israel and South Korea. The main question the researchers

aimed to address was whether exercise can help to prevent colon cancer from coming back. After chemotherapy, the participants were randomly assigned to one of two groups. One group experienced the current standard of care which is essentially receiving a book that tells you to eat well and exercise, and the other group was assigned a personal trainer for three years. The personal trainer's job was to come up with an exercise plan that was tailored to the individual to keep them moving and motivated about it. Indeed, patients with the personal trainer were exercising more than patients receiving the current standard of care. The study's researchers are hoping that with promising results from their clinical trial, more individuals will be inspired to reconsider the survival benefit that exercise has to offer in long-term cancer treatment.

https://www.ctg.queensu.ca/cctg_news/strengthening-body-prevent-colon-cancer-returning

13. How high-fat diet impacts colorectal cancer (Jul 6/17)

In a recently published study, researchers have discovered a specific molecular pathway that plays a role in the link between a high-fat diet and cancer development in the colon. The study showed that cancer stem cell growth in the colon was sped up in the presence of high-fat Western diet conditions. The researchers found that when the JAK2-STAT3 cellular signalling pathway was blocked, an important pathway involved in tumour proliferation, the rise in cancer stem cell growth stimulated by the high-fat diet declined. While the impact of diet on colorectal cancer is well known, these study findings shed light on the specific molecular pathway and high-fat intake. From here, further research may be done in order to pinpoint the exact mechanism of the association in order to develop therapeutics to counteract or minimize the negative effects of the Western diet on colorectal cancer. Changes in lifestyle habits, including the adoption of a healthy, balanced diet rich in good fats, remain an essential part of addressing the problem at its cause.

https://www.sciencedaily.com/releases/2017/07/170706121221.htm

14. Grape-based compounds kill colon cancer stem cells in mice (Jun 19/17)

Researchers have found that a compound found in grape skins and seeds – resveratrol – could eventually be developed into a treatment to help prevent colon cancer. For the animal study, mice with colon cancer tumours were separated into 3 groups: a control group, a group fed resveratrol and a group fed sulindac, an anti-inflammatory drug previously shown to significantly reduce the number of tumours in humans. Researchers found that the incidence of tumours was reduced in the mice consuming resveratrol by 50%, similar to the group which consumed the diet supplemented with sulindac. The researchers found that when combined with grape seed extract, resveratrol is even more effective at eradicating colon cancer cells. It was observed that resveratrol and grape seed extract are not as effective at suppressing cancer stem cells when taken in separate low doses compared to when they are combined and taken together. Unlike chemotherapy, the combination of these compounds is not toxic to healthy cells. These findings are exciting as they could potentially lead to a combination of the compounds in a pill form to be taken as a preventative method for colon cancer as well as to reduce the risk of recurrence of the disease among survivors. The combination of compounds specifically target cancer stem cells, which are capable of self-renewal, cellular differentiation and maintain their stem cell-like characteristics even after invasion and metastasis. Researchers suggest that if successful in human trials, the combination could be taken in low doses using currently available supplements for grape seed extract and resveratrol.

https://www.sciencedaily.com/releases/2017/06/170619101829.htm

Image from: https://assets.copdnewstoday.com

OTHER

15. Common causes of death predominate among long-term colorectal cancer survivors (May 25/17)

A large cohort study surveyed more than 139,000 patients with a colorectal cancer (CRC) diagnosis and found that 95% of all deaths from the disease occurred in the first 5 years after diagnosis. It was found that CRC deaths plateau over time, and then other causes of death become more important as patients survive longer. Beyond the 5-year survival period, patients were increasingly likely to die from causes that are common in the general population, emphasizing the importance of lifestyle modification in the prevention of cardiovascular (most prevalent at the 8-year survival mark) and second primary cancers and neurologic diseases (prevailed at the 10 year survival mark). The study data support the American Cancer Society's recommendations for survivorship care including cancer screening programs, dietary and exercise recommendations and smoking and alcohol reduction. Researchers emphasize that cancer survivors have unique health problems, suffering from the consequences of treatment as well as exposure to risk factors that are linked to other diseases. Researchers also found that the trends differed by age - among patients below the age of 65 at diagnosis, CRC remained the leading relative cause of death until 11 years, at which second primary cancers became the leading cause of death. In comparison, among patients aged 80 or older at diagnosis, CRC was the leading relative cause of death until 3 years, after which cardiovascular disease became the leading cause of death. The researchers stress the importance of patient counselling in survivorship care, a process they believe should begin at the moment of diagnosis.

http://www.ascopost.com/issues/may-25-2017/common-causes-of-death-predominate-among-long-term-colorectal-cancer-survivors/

16. ASCO 2017: Impact of patient age on molecular alterations in colorectal tumours (Jun 7/17)

According to a new study, it was found that younger patients who are diagnosed with colorectal cancer (CRC) appear to have more than three times as many mutations in their tumours compared to older patients, a detail that could help better streamline treatment strategies. It was discovered that tumour mutation load and gene mutations which are important in DNA repair were more prevalent among younger patients. This research is relevant in a time when CRC incidence is on the rise in patients 45 years or younger. The lead investigator of the study indicates that while it may seem counterintuitive to see tumours with high mutation loads as a positive, it may actually improve the way some therapies work. For example, CRC immunotherapies boost the body's immune response. When a cell has more mutations, it will "stand out" even more to the immune system, making it more likely to be targeted and destroyed. The study findings revealed that high mutation load was found in 8.2% of young patients vs. 2.6% of older patients. Researchers reiterate the hypothesis that CRC rates are increasing in younger patients due to lifestyle factors such as diet and exercise. Furthermore, many studies are currently being focused on the role of bacteria and local inflammation in the colon as a predisposing factor in cancer development. With the discovery that these same young patients also tend to have a greater tumour mutation load, the link between high mutation load and lifestyle factors is open for further exploration.

http://www.ascopost.com/News/55721