Perspectives from
Gastrointestinal Cancers Symposium

Colorectal cancers show ‘continuum’ of molecular variances
Knowledge may lead to tailored therapy

Disparities affect young patients with gastric cancer
Impact of racial, ethnic discrepancies requires additional research

Nivolumab improves OS, PFS in advanced gastrointestinal cancers
Phase 3 study indicates nivolumab could be ‘new treatment option’

Aspirin reduces colorectal cancer risk, increases risk for GI bleeding
Guest commentary reviews benefits, drawbacks of aspirin as prevention
Not all cancer cells within a tumor are equal

Despite current advances in cancer therapy, tumor recurrence and metastases remain clinical challenges. A potential new approach to address these is the targeting of a subset of the tumor cell population known as cancer stem cells (CSCs). CSCs are highly tumorigenic, have high metastatic potential, and are resistant to conventional cancer therapies.

CSCs may drive tumor growth

Stemness is defined by the ability to self-renew and differentiate. Unlike normal stem cells, which differentiate into healthy, mature cells, CSCs differentiate into cancer cells. The stemness of CSCs is maintained by various signaling pathways that are overactivated, including JAK/STAT, Wnt/β-catenin, Nanog, and Notch, depending on the tumor type. 

Stemness may enable CSCs to metastasize and regrow tumors. This makes CSCs phenotypically different from non-stem cancer cells and may confer therapy resistance. Stemness can be acquired by non-stem cancer cells as they dedifferentiate in response to multiple stimuli, possibly including conventional cancer therapies.

The CSC model may help explain tumor recurrence

In the clonal evolution model, all cells within a malignant tumor have similar tumorigenic activity. By contrast, in the CSC model only a subset of tumor cells, CSCs, have tumor-initiating capability. This may help to explain why early tumor shrinkage is often poorly predictive of overall survival. While conventional therapies kill bulk of non-stem cancer cells, resulting in tumor shrinkage, CSCs may remain viable and later reestablish the tumor, leading to relapse.

A key implication of the CSC model for cancer therapy is that both CSCs and non-stem cancer cells should be targeted to reduce tumor recurrence and metastasis. 

The next generation of cancer therapeutics is in development with investigational agents designed to inhibit stemness pathways.

STEMNESS PATHWAYS

CANCER STEM CELLS

CSCs are highly tumorigenic, have high metastatic potential, and are resistant to conventional cancer therapies.

RECURRING TUMOR

GI Cancers Symposium highlights treatment advances, role of patient characteristics

Recent research and treatment trends in colorectal, esophageal, gastric, gastroesophageal junction and neuroendocrine cancers were highlighted during this year’s Gastrointestinal Cancers Symposium, held in San Francisco under the theme “Multidisciplinary Precision Care: Progress and Innovation.”

Gastroenterologists, oncologists and surgeons gathered from January 19-21 to discuss the management of gastrointestinal cancers. Results from a large cohort of Asian patients demonstrated that nivolumab improved OS, PFS and overall response rates when used as salvage therapy in pre-treated, advanced gastric or gastroesophageal junction cancer. Aspizin was found to be protective against the development of colorectal cancer, although this benefit must be weighed against the increased risk of gastrointestinal bleeding. Two separate studies showed that patient demographics — including race, ethnicity, age and socioeconomic status — affect outcomes in gastric cancer, and another trial examined the use of microsatellite instability testing in younger patients with colorectal cancer.

HemOnc Today was onsite at the Gastrointestinal Cancers Symposium, attending sessions and speaking with experts. This supplement, which also includes reporting from Healive Gastroenterology, provides an overview of the most noteworthy findings and includes physician perspectives to provide further insight into the impact these findings may have in everyday practice. — The Publishers of HemOnc Today

WEB WATCH

Research highlights strategies for personalized treatment

Additional findings presented at the Gastrointestinal Cancers Symposium demonstrated that patients with metastatic colorectal cancer who engaged in moderate exercise for at least 30 minutes a day experienced reduced risk for cancer mortality and progression. To read this article, and the full articles summarized below, please visit Healive.com/Hematology-Oncology.

PET scans can offer alternative route for treatment of esophageal cancer

PET scans used to assess response to initial chemotherapeutic algorithms allowed clinicians to tailor additional treatments, leading to a nearly 10-percentage point increase in complete response rates for patients who switched to an alternative chemotherapy following a PET scan compared with patients who continued the initial chemotherapy.

Watch-and-wait approach may be alternative to surgery for certain patients with rectal cancer

Patients with rectal cancer who achieve a clinical complete response may be able to follow a watch-and-wait approach rather than undergo surgery. Individuals who received “watch-and-wait” care achieved a 3-year OS rate comparable to historical data from those who underwent surgery.

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Rectal, left-sided colon cancers show a continuum of molecular variances

Rectal and left-sided colon cancers are not clearly delineated by location but, rather, are characterized by a range of distinct molecular variations, which has implications for developing tailored treatments in the future, according to data presented at the Gastrointestinal Cancers Symposium.

“Colorectal cancers carry a continuum of molecular alterations from the right to the left side, rather than displaying sharp, clear-cut differences according to location,” Mohamed E. Salem, MD, gastrointestinal oncologist, assistant professor of clinical medicine, and Associate Fellowship Program Director in the division of hematology and oncology at Lombardi Comprehensive Cancer Center, Georgetown University, told Healio Gastroenterology.

To better define the molecular differences between left-sided colon tumors and rectal tumors, Salem and colleagues used protein expression, gene amplification and Next-Gen sequencing to evaluate these differences in 1,457 tumors originating in the splenic flexure to the descending colon, the sigmoid colon, or the rectum. They also used polymerase chain reaction to measure microsatellite instability (MSI) and somatic nonsynonymous missense mutations to calculate tumor mutational load.

“For instance, the incidence of MSI significantly decreased when moving from the right-side colon (22%), to descending colon (7%), to the sigmoid (4%) and on to the rectum (1%; P = .015),” Salem said. “And although HER-2 overexpression and amplification did not vary significantly across left-sided tumor locations, HER-2 amplification was more common in rectal compared with right-side colon tumors (5.4% vs. 1.3%; P = .0328).”

Rectal tumors had a higher frequency of TP53 and APC compared with tumors originating in the splenic flexure to the descending colon; lower frequencies of PIK3CA, BRAF, GNAS, HNF1A and CTNNB1; and higher expression of TOP2A, ERCC1 and MGMT.

Tumor mutational load was highly concordant with MSI across tumor types. Additionally, PD-1 and tumor mutational load correlated in rectal tumors but not in other tumor types.

“It is possible that moving forward, comprehensive molecular testing will help us to better understand disease biology and mechanisms of resistance to treatment, as well as allowing us to better stratify patients, thus enabling a transition from one-size-fits-all — generally ineffective — treatment to individually tailored therapy,” Salem said.

Disclosure: Salem reports no relevant financial disclosures.


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Rectal, left-sided colon cancers show a continuum of molecular variances

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Racial, ethnic disparities identified in young gastric cancer patients

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– by Adam Leitenger

Disclosure: The researchers report no relevant financial disclosures.


Disclosure: Salem reports no relevant financial disclosures. Please see the study abstract for a list of all other researchers’ relevant financial disclosures.
Cabozantinib demonstrates efficacy in carcinoid, pancreatic neuroendocrine tumors

The trial included 41 patients with carcinoid tumors and 20 patients with pancreatic neuroendocrine tumors. The median age of patients with carcinoid tumors was 63 years and 44% were men; 51% of patients had an ECOG performance status of 0 and 49% had an ECOG performance status of 1.

Partial responses were achieved by 3 patients with pancreatic neuroendocrine tumors (ORR, 15%; 95% CI, 5-36) and 6 patients with carcinoid tumors (objective response rate, 15%; 95% CI, 5-36). Median PFS for these 2 subgroups was 8.5 months (95% CI, 8.5 months-not reached) among patients with carcinoid tumors.

Grade 3 to grade 4 adverse events included hypertension (13%), hypophosphatemia (11%), diarrhea (10%), increased lipase or amylase (8%), lymphopenia (7%), thrombocytopenia (5%) and fatigue (5%).

While dose reduction was common, treatment was “tolerable,” the researchers wrote.

“Treatment with cabozantinib was associated with objective tumor responses in both carcinoid and pancreatic neuroendocrine tumors,” Chan said. “The toxicity profile that we observed is consistent with what has been reported with cabozantinib in other disease settings. It will be important to confirm the activity of cabozantinib in a randomized phase 3 study.” — by Julia Ernst, MS

Analysis supports use of ramucirumab across age groups in gastric cancer

Ramucirumab as monotherapy and in combination with paclitaxel appears to be safe and effective for advanced gastric cancer across all age groups, according to a subgroup analysis of the REGARD and RAINBOW trials presented at the Gastrointestinal Cancers Symposium.

“Almost two-thirds of patients with gastric cancer are diagnosed over the age of 65, and more than half of those patients are over 75,” Kei Muro, MD, of the Aichi Cancer Center Hospital in Nagoya, Japan, said during his presentation. “Elderly patients aged 75 and older are underrepresented in clinical trials, but one-third of the patients in these two studies were 65 and older. Both studies demonstrated statistically significant, and clinically meaningful, prolongations of PFS and OS. We sought to explore the efficacy of ramucirumab [Cyramza, Eli Lilly] in different age groups.”

Patients in both phase 3 trials were randomly assigned to treatment with ramucirumab or placebo in the second-line setting. Patients in the REGARD trial were randomly assigned 1:1 to treatment with ramucirumab 8 mg/kg plus paclitaxel or placebo plus paclitaxel. Kaplan-Meier analysis and Cox proportional hazards regression were conducted to examine OS and PFS.

Muro and colleagues looked at the results in each study according to age (less than or equal to 45 years, 45 to 70 years, greater than or equal to 70 years and greater than or equal to 75 years; see Table). A subpopulation treatment effect pattern plot (STEPP) was used to evaluate efficacy and the rate of adverse events across age subgroups.

“The key baseline demographics are mostly consistent across age groups,” Muro said. “The majority of participants were in the subgroup of patients aged 45 to 70 years. The subgroup of patients aged 75 and older had a very small number of individuals.”

**Treatment with ramucirumab across age groups**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Number of patients</th>
<th>Median OS (months)</th>
<th>HR (95% CI) REGARD</th>
<th>Median PFS (months)</th>
<th>HR (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>≤45</td>
<td>28</td>
<td>5.8</td>
<td>0.59 (0.27, 1.26)</td>
<td>1.9</td>
<td>0.58 (0.27, 1.26)</td>
</tr>
<tr>
<td>45-70</td>
<td>12</td>
<td>2.9</td>
<td>0.78 (0.57, 1.06)</td>
<td>2.2</td>
<td>0.45 (0.34, 0.61)</td>
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<tr>
<td>≥70</td>
<td>115</td>
<td>4.1</td>
<td>0.73 (0.44, 1.23)</td>
<td>2.1</td>
<td>0.56 (0.34, 0.92)</td>
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<tr>
<td>≤45</td>
<td>37</td>
<td>5.9</td>
<td>0.61 (0.33, 0.93)</td>
<td>3.9</td>
<td>0.50 (0.30, 0.83)</td>
</tr>
<tr>
<td>45-70</td>
<td>37</td>
<td>3.8</td>
<td>0.60 (0.70, 1.06)</td>
<td>2.8</td>
<td>0.65 (0.53, 0.79)</td>
</tr>
<tr>
<td>≥70</td>
<td>68</td>
<td>2.8</td>
<td>0.88 (0.60, 1.28)</td>
<td>4.7</td>
<td>0.68 (0.47, 0.97)</td>
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STAT3 is a transcription factor that, when overactivated, becomes an oncogenic signaling hub that promotes the stemness of cancer stem cells (CSCs), suppresses antitumor immunity, and drives tumor-promoting inflammation.1,2

**STAT3 is overactivated in CSCs**

In normal cells, STAT3 is activated in a strictly regulated and transient process, and its signaling is involved in physiological functions, including development, differentiation, immunity, and metabolism.1 However, when STAT3 signaling is overactivated, it can drive the development and progression of tumors.1 STAT3 is constitutively active in CSCs and may be critical for maintaining their stemness.2 During progression of tumors,5 STAT3 is overactivated, and it can drive the development and progression of tumors.5 STAT3 mediates multiple downstream effects, including increased expression of genes that maintain stemness, support CSC proliferation and survival, and promote metastasis and tumor immune evasion.6,7

**STAT3 mediates downstream effects that promote stemness**

STAT3 receives upstream activating signals from the interaction of CSC surface receptors with various molecules, including growth factors (eg, epidermal growth factor, platelet-derived growth factor, platelet-derived growth factor alpha [TGF-α]) and proinflammatory cytokines (eg, interleukin 6 [IL-6]).4 Binding of other factors to G-protein–coupled receptors and Toll-like receptors is also known to activate STAT3.2

When a ligand binds to a receptor, JAK enzymes associated with the receptor become phosphorylated, which in turn leads to phosphorylation of inactive STAT3. Phosphorylated STAT3 then dimerizes into its active form. Activated STAT3 translocates into the CSC nucleus, where it binds to promoters in DNA1 and participates in crosstalk with other stemness signaling pathways, including Nanog, Notch, and β-catenin.1,8 Thus, STAT3 mediates multiple downstream effects, including increased expression of genes that maintain stemness, support CSC proliferation and survival, and promote metastasis and tumor immune evasion.6,7

**STAT3 may suppress antitumor immunity and drive tumor-promoting inflammation**

STAT3 has been shown to suppress antitumor immunity, particularly by antagonizing the effects of nuclear factor-kappa B (NF-κB). STAT3 can reduce NF-κB–mediated expression of antitumor T helper type 1 (TH1) cytokines, which are necessary for both innate and T cell–mediated immune responses.1,2

In addition to its critical role in tumor immune evasion,1 STAT3 also drives tumor-promoting inflammation by increasing the expression of proinflammatory cytokines such as IL-6. These cytokines in turn bind to receptors, including CSC surface receptors, and lead to further activation of STAT3, resulting in an inflammatory positive feedback loop.2,13

**STAT3 may increase metastatic potential by promoting epithelial-mesenchymal transition (EMT)**

To metastasize, a cancer cell must first invade locally, enter the bloodstream, and colonize at a distant organ. These steps involve the reactivation of a developmental process known as EMT, which may be needed to initiate metastasis of CSCs, which in turn may inhibit their tumorigenicity, metastatic potential, and resistance to conventional cancer therapies. Except during embryonic development, STAT3 inhibition has not been found to influence the growth or survival of normal cells, suggesting that off-target effects may be minimized.2,14

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**References:**
Nivolumab appears safe, effective in patients with advanced gastrointestinal cancers

Nivolumab demonstrated improvements in OS, PFS and overall response rate when used as salvage therapy for patients with pretreated, advanced gastric or gastroesophageal junction cancer, according to findings presented at the Gastrointestinal Cancers Symposium.

"Recent clinical trials have established first- and second-line chemotherapy as the standard treatment for advanced gastric or gastroesophageal junction cancer," the researchers wrote. "However, the prognosis of advanced gastric or gastroesophageal junction cancer is still poor."

Phase 1 and 2 studies of immune checkpoint inhibitors, including nivolumab (Opdivo, Bristol-Meyers Squibb), have demonstrated activity in gastric cancer. Yoon-Koo Kang, MD, PhD, professor of medicine in the department of oncology at Asian Medical Center at University of Ulsan College of Medicine in Seoul, South Korea, said in a presentation. However, the effect of nivolumab has not yet been established in a randomized, controlled study.

Kang and colleagues evaluated the safety and efficacy of this agent as salvage therapy in patients with advanced gastric or gastroesophageal junction cancer who had failed standard chemotherapy. Patients were eligible for the study if they were 20 years of age or older, had an ECOG performance status of 0 to 1 and had failed two or more previous chemotherapy regimens.

"About 20% of patients had 2 prior treatment failures and 40% of patients had 3 regimen failures," Kang said during his presentation. "Another 40% of patients had failed 4 or more prior treatment regimens."

Patients (n = 493) were randomly assigned 2:1 to receive 3 mg/kg nivolumab (n = 330) or placebo (n = 163) every 2 weeks until unacceptable toxicity or disease progression. The primary end point was OS in the intention-to-treat population.

Median OS was 5.32 months among patients treated with nivolumab compared with 4.11 months for patients receiving placebo (HR, 0.63; 95% CI, 0.50-0.78) at data cutoff, which was 5.6 months after the last patient was randomly assigned. OS rates were higher for patients receiving nivolumab than placebo at both 6 months (46.4% vs. 34.7%) and 12 months (26.6% vs. 10.9%).

The overall response rate with nivolumab was 11.2% (95% CI, 7.7-15.6) compared with 0% for placebo (95% CI, 0.0-2.8).

Disclosure: Kang reports an investigator role on a separate trial of nivolumab. Funding for that clinical trial is provided to his institution.

Younger age affects OS, demographics in gastric adenocarcinoma

Younger age served as an independent predictor of improved OS among patients with gastric adenocarcinoma, according to findings presented at the Gastrointestinal Cancers Symposium.

In addition, younger patients tended to be more ethnically diverse and have decreased socioeconomic status.

"Recent foreign publications have demonstrated increasing frequencies of gastric cancer in younger patients, with differing biology and outcomes," the researchers wrote. "This study … aims to examine disparities and the impact of age on OS."

Shrawan G. Gaitonde, MD, a fellow at the John Wayne Cancer Institute, and colleagues examined data from the National Cancer Data Base. The researchers collected information about demographics, tumor characteristics and treatment for all patients diagnosed with primary gastric adenocarcinoma from 2004 to 2013. Patients were grouped according to age (adolescents and young adults (AYA), < 40 years; adults, ≥ 40 years).

Five-year OS was 32.9% among AYAs compared with 24.9% among older adults (< .001). After correcting for significant competing factors, higher tumor grade (HR, 1.61; 95% CI, 1.32-1.97), distant metastases (HR, 2.22; 95% CI, 1.84-2.60) and increasing tumor (HR, 2.69-5.44) and nodal stage (HR, 1.84-2.35) independently reduced OS in AYAs. Hispanic (HR, 0.78; 95% CI, 0.65-0.93) or Asian ethnicity (HR, 0.72; 95% CI, 0.56-0.93) and receipt of adjuvant chemotherapy (HR, 0.62; 95% CI, 0.52-0.75) enhanced OS.

Comparable results were observed among older adults, although all markers of low socioeconomic status resulted in decreased OS. Younger age (< 40 years) demonstrated an independent improvement on OS only in early-stage disease (stage 1/2); this resulted in a survival advantage of 19% (HR, 0.81; 95% CI, 0.71-0.93) compared with older adults.

"Further research is needed to address whether national screening strategies could improve survival for selected young patients," the researchers wrote.

Disclosure: The researchers report no relevant financial disclosures.

Nivolumab continued from page 10

receiving placebo (HR, 0.63; 95% CI, 0.50-0.78) at data cutoff, which was 5.6 months after the last patient was randomly assigned. OS rates were higher for patients receiving nivolumab than placebo at both 6 months (46.4% vs. 34.7%) and 12 months (26.6% vs. 10.9%).

The overall response rate with nivolumab was 11.2% (95% CI, 7.7-15.6) compared with 0% for placebo (95% CI, 0.0-2.8).

Median PFS was 1.61 months with nivolumab and 1.45 months with placebo (HR, 0.60; 95% CI, 0.49-0.75). Drug-related adverse events of grade 3 or higher were observed in 11.5% of patients treated with nivolumab and 5.5% of patients treated with placebo. The rate of treatment discontinuation due to drug-related adverse events of any grade was 2.7% among patients receiving nivolumab and 2.5% among patients receiving placebo.

"This phase 3 study demonstrated the efficacy and safety of nivolumab in later-line treatment for patients with advanced gastric cancer. Treatment-related adverse events leading to discontinuation or death were very rare, and there was no difference between the two arms," Kang said. "The results indicate that nivolumab could be a new treatment option for patients with advanced gastric cancer."

Disclosure: Kang reports consultant or advisory roles with ImClone Systems, a wholly owned subsidiary of Eli Lilly and Company, Novartis, Ono Pharmaceutical Company, Roche/Genentech and Taiho Pharmaceutical, and research funding from Bayer, Novartis and Roche/Genentech. Please see the full list for all of other researchers' relevant financial disclosures.


Younger age affects OS, demographics in gastric adenocarcinoma

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Aspirin linked to increased GI bleeding risk, reduced colorectal cancer risk

L
ong-term use of aspirin was asso-
ciated with a reduced risk for colorectal cancer, but an in-
creased risk for gastrointestinal bleeding, highlighting the need to weigh the risks and benefits of prophylactic aspirin use, according to study results presented at the Gastrointestinal Cancers Symposium.

Because data comparing the risks and benefits of long-term aspirin use are limited, Joseph Sung, MD, PhD, and Kevin K. F. Tsoi, PhD, of The Chinese University of Hong Kong, performed a population-based cohort study involving “a large group of 206,243 aspirin users compared with 482,966 non-users [who] were followed up to 14 years to document the incidence and mortal-
ity of colorectal cancer and gastrointestinal bleeding, which might be related to the use of aspirin,” Sung told Healio Gastroenterology.

The aspirin users took daily aspirin for at least 6 months (mean dose, 80 mg per day; mean duration, 7.7 years), and the controls were matched by age and sex.

Overall, 5,776 (2.8%) of the aspirin users received a colorectal cancer diagnosis, and 2,097 (1.02%) died of colorectal cancer. In comparison, 16,483 (3.41%) controls received a colorectal cancer diagnosis, and 7,966 (1.65%) died of colorectal cancer.

Cox-proportional hazard regression analysis showed aspirin use was associated with “a modest but significant” reduced risk for colorectal cancer-related mortality (HR = 0.65; 95% CI, 0.62-0.69). “Aspirin reduced colorectal cancer mortality by 35%,” Sung said.

However, 11,187 (5.42%) of aspirin users had gastrointestinal bleeding, and 841 (0.41%) died. In comparison, 15,186 (3.14%) controls had gastrointestinal bleeding, and 1,682 (0.35%) died.

Cox-proportional hazard regression analysis showed aspirin use was also associated with “a modest but significant” increased risk for mortality related to gastrointestinal bleeding (HR = 1.24; 95% CI, 1.14-1.35).

“Aspirin increased bleeding-related mortality by 24%,” Sung said. “We conclude that aspirin as a prophylactic medication is a two-edged sword. Considerations of prophylactic use should balance the benefit and the risk of this medication in specific populations.”

– by Adam Leitenberger

Reference:

Disclosures: The researchers report no relevant financial disclosures.

Analysis continued from page 7

als, and the placebo arm of this subgroup had fewer patients. As a result, there are some imbalances between treatment arms.

Results of the STEPP analysis demonstrated no clear patterns with regard to age for differential risks related to the efficacy of ramucirumab or adverse events — of any grade or equal to grade 3 or above — according to age. Muro highlighted the similar

discussion confirmed the use of ramucirumab for the treatment of patients with gastric cancer regardless of age.”

– by Julia Ernst, MS

Reference:

Disclosures: Muro reports receiving honoraria from Chugai Pharma, Merck Serono, Taiho Pharmaceutical, Takeda and Yakult Honsha. Please see the full study for a list of all other researchers’ relevant financial disclosures.

Guest Commentary: Aspirin as prevention requires assessment of benefits, drawbacks

Editor’s note: In this guest commentary, Jimmy Hwang, MD, FACP, a medical oncologist at the Levine Cancer Institute, discusses the role of aspirin in the prevention of colorectal cancer following a presentation on the topic at the Gastrointestinal Cancers Symposium. Joseph Sung, MD, PhD, and Kevin K. F. Tsoi, PhD, of The Chinese University of Hong Kong, demonstrated that long-term aspirin use was associated with a reduced risk for colorectal cancer, but an increased risk for gastrointestinal bleeding.

The results from Sung and Tsoi are in line with earlier studies that examined the role of aspirin as prevention in colon cancer. There have been several randomized clinical trials investigating the role of aspirin — either at 81 milligrams or 300 to 325 milligrams per day — that have demonstrated that aspirin does prevent the development of colon adenomas. It is presumed that the prevention of colon adenomas is a precursor to preventing colon cancer, thereby leading to the use of aspirin as a preventative tool.

The study from Sung and colleagues reinforces the notion that we can prevent colon cancer by preventing colon polyps.

The use of aspirin as prevention can be broken down into two different groups. The data are strongest for patients who have had colon cancer previously. Some of the data regarding COX-2 inhibitors, such as sulindac, are also robust in patients with certain familial polyposis syndromes. This kind of data supports the benefit of prevention in those groups. The key question relates to sporadic patients — individuals who don’t have a known family history or predisposition.

In this abstract, the decrease in risk of colon cancer and improvement in outcomes are relatively modest. In absolute terms, it was about one half of one percent. The odds ratio is more impressive statistically, demonstrating about a 35% decrease in colorectal cancer-related mortality. However, in absolute terms, it’s a relatively small difference.

That said, there are patients with an increased risk for colorectal cancer for familial reasons or, in particular, among those who have had colon cancer previously. In these patients, the risk of recurrence is higher, so the chances for benefit are higher. Thus, there is a greater tendency to recommend the use of aspirin in that population.

Gastrointestinal bleeding is the primary reason aspirin is not recommended for colon cancer prevention. This risk is real. The risk for gastrointestinal bleeding from aspirin is not as high as the benefit of receiving aspirin, although it’s also not that far off in absolute terms.

A report from the U.S. Preventive Services Task Force that was published last summer discussed the use of aspirin for colorectal cancer prevention. Gastrointestinal bleeding is the reason they do not universally recommend aspirin for colon cancer prevention. However, the report acknowledges that there is some benefit.

Therefore, it should be a nuanced discussion about the risks and benefits of aspirin. In people who have a history of bleeding or ulcers, one may be less inclined to recommend aspirin as prevention unless their risk for colon cancer is particularly high. In this case, family history and the patient’s personal history are important to consider. If the patient has a history of polyps, or colon cancer, that’s going to affect your calculations.

However, it should be emphasized that there is a clear statistical benefit to using aspirin as prevention for colon cancer — it’s just not a high-frequency benefit in terms of numbers of patients. The same thing is true for the risk of bleeding — it’s not a high-frequency event, but it’s a real event that must be considered.

– by Jimmy Hwang, MD, FACP

Reference:

Disclosures: Hwang reports no relevant financial disclosures.
Revised guidelines stand to increase uptake of routine MSI testing

Significant underuse of routine testing for microsatellite instability demonstrates the importance of updated National Comprehensive Cancer Network guidelines recommending universal testing. A two-year analysis assessing uptake of routine testing from 2010 to 2012, before the revised guidelines were published, shows approximately half of eligible patients underwent screening, according to data presented at the Gastrointestinal Cancers Symposium.

“At that point, not all patients with colorectal cancer — including young people — were screened for MSI,” Talha Shaikh, MD, of Fox Chase Cancer Center, told HemOnc Today. “As of 2014, national guidelines — including ones from the NCCN, which seem to be the most commonly adopted source of guidelines in the United States — state that everyone should be tested for MSI.”

The researchers, led by Nestor F. Espaola, MD, MPH, associate director of cancer health disparities and community engagement and professor of surgical oncology at Fox Chase, used the National Cancer Data Base to identify patients aged 18 to 49 who were diagnosed with invasive colorectal adenocarcinoma — and whose MSI testing status was known — between 2010 and 2012. Multivariable logistic regression was used to determine independent factors that correlated with receipt of MSI testing and MSI-high (MSI-H) status in patients who were tested.

The researchers identified 17,218 patients. Although 43% of patients (n = 7,422) were tested for MSI, the number of patients tested increased between 2010, when 36% were tested, and 2012, when 48% were tested (P < .001). Independent factors that correlated with MSI testing included a higher education level, early stage disease and the number of lymph nodes examined (≥12). Older age (40 to 49 years), Hispanic ethnicity, not having private insurance, not receiving care in an academic or research facility, location of the rectosigmoid tumor, and unknown insurance status; older age (40 to 49 years), female gender, non-malignant histology, adenoma detection when treated with the selective cyclooxygenase-2 inhibitor celecoxib, and having a higher personal or family history of colorectal cancer were independently associated with MSI-H status — will remain an issue.

In their conclusion, the researchers write that interventions to “improve adherence to guideline-based care” are needed, especially among patients at greater risk for MSI-H disease. — by Julia Ernst, MS

Reference:
Disclosure: Shaikh reports no relevant financial disclosures.

Enzymes may predict efficacy of celecoxib in preventing colorectal adenomas

Immunochemistry was effective for determining which patients with pre-malignant colorectal adenomas may benefit from celecoxib to prevent malignant progression, according to findings presented at the Gastrointestinal Cancers Symposium.

“The APC trial showed that patients at high risk for colorectal adenoma development experienced a 33% to 45% reduction in postpolypectomy adenoma detection when treated with the selective cyclooxygenase-2 inhibitor celecoxib,” the researchers wrote. “Celecoxib inhibits expression of prostanoid E2, an inflammatory mediator produced by fatty acid metabolism via cyclooxygenases, and is degraded through the activity of 15-prostaglandin dehydrogenase.”

Jiping Wang, MD, PhD, surgical oncologist at Dana-Farber Cancer Institute and assistant professor of surgery at Harvard Medical School, and colleagues used immunochemistry to analyze expression of COX-2 and 15-prostaglandin dehydrogenase in adenomas taken from patients in the APC trial prior to treatment. Expression of COX-2 was graded as high vs low and expression of 15-prostaglandin dehydrogenase was determined to be present or absent.

The researchers used a combined variable to determine tumor prognosis. MSI-H levels. Low was determined to be COX-2 low/15-prostaglandin dehydrogenase present; High was classified as COX-2 high/15-prostaglandin dehydrogenase absent; or COX-2 low/15-prostaglandin dehydrogenase absent.

Outcome data were available for biomarker determinations in 71% of patients (n = 1,295).

Celecoxib provided the greatest decrease in risk among patients whose adenomas had elevated levels of COX-2 at baseline (RR = .37; P = .001). This decline was less significant among patients in the low COX-2 category (RR = .64).

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facility, location of the rectosigmoid/rectal tumor, non-mucinous histology, tumors of an unknown grade and not undergoing definitive surgery all predicted underuse of MSI testing.

MSI-H disease was detected in 531 (8%) of 6,258 patients tested whose MSI status was known. Lower income, prior cancer and stage 2 disease were independent predictors of MSI-H status: older age (40 to 49 years), female gender, greater comorbidity, receiving care in a non-metropolitan facility, facility location, distal tumor location, non-mucinous histology, unknown/ lower tumor grade, and not receiving chemotherapy were all inversely associated with MSI-H status.

Shaikh and colleagues were “surprised” by how few people underwent testing, even after considering the increase in patients tested for MSI between 2010 and 2012. “Our results paint a somewhat grim picture, with only about 50% of patients receiving screening,” he said. “Hopefully, now that everyone should be screened for MSI, we do a good job adhering to guidelines and the number of patients being screened will improve.”

However, even as screening increases, Shaikh believes disparities — including insurance and socioeconomic status — will remain an issue.

In their conclusion, the researchers write that interventions to “improve adherence to guideline-based care” are needed, especially among patients at greater risk for MSI-H disease. — by Julia Ernst, MS

Reference:
Disclosure: Shaikh reports no relevant financial disclosures. Please see the full study for a list of all other researchers’ relevant financial disclosures.
STAT3 is a transcription factor that, when overactivated, becomes an oncogenic signaling hub that promotes the stemness of cancer stem cells (CSCs), suppresses antitumor immunity, and drives tumor-promoting inflammation.1,2

**STAT3 is overactivated in CSCs**

- In normal cells, STAT3 is activated in a strictly regulated and transient process4
- However, when STAT3 signaling is overactivated, it can drive the development and progression of tumors5
- STAT3 is constitutively active in CSCs and may be critical for maintaining their stemness, the ability to self-renew and differentiate3,6
- CSCs are highly tumorigenic with high metastatic potential, and they are more resistant to conventional therapies than non-stem cancer cells in tumors3,7

**STAT3 mediates downstream effects that promote stemness**3,8

- STAT3 receives upstream activating signals from the interaction of CSC surface receptors with various molecules, including growth factors and proinflammatory cytokines6
- Activated STAT3 translocates into the CSC nucleus9 and participates in crosstalk with other stemness signaling pathways10,11
- Thus, STAT3 mediates multiple downstream effects, including increased expression of genes that maintain stemness3,8

**STAT3 may suppress antitumor immunity and drive tumor-promoting inflammation**12

- STAT3 has been shown to suppress antitumor immunity, particularly by antagonizing the effects of nuclear factor-kappa B (NF-kB) that support both innate and T cell–mediated immune responses12
- STAT3 also drives tumor-promoting inflammation by increasing the expression of proinflammatory cytokines such as IL-62,12
- These cytokines in turn bind to receptors, including CSC surface receptors, resulting in an inflammatory positive feedback loop2,12

**STAT3 is an important potential target for cancer therapy**12

Current research suggests that targeting STAT3 may inhibit stemness of CSCs, which in turn may inhibit their tumorigenicity, metastatic potential, and resistance to conventional cancer therapies.3,8