GASTRIC CANCER

SANDRA E. KURTIN, RN, MS AOCN, ANP-C Our next lecture is on the Collaborative Management of Patients with Gastric Cancer. Please join me in welcoming Dr. David Ilson from Memorial Sloan Kettering Cancer Center and my friend and colleague, Steve Malangone, who I work with at the University of Arizona Cancer Center. Welcome.

DR. ILSON Good morning and welcome to this session about the Collaborative Management of Patients with Gastric Center. We're going to review today management of advanced disease, as well as neoadjuvant and adjuvant therapies. And I think we also have some cases.

The objectives today are to manage patients with advanced gastric cancer to try and improve patient outcomes, but also to anticipate and address treatment-related side effects associated with current and emerging therapies and to provide direct care for patients with advanced gastric cancer regardless of the practice setting, including knowing when to refer patients from the community to a more specialist center. Then we'll talk about mechanism of action of some of the emerging targeted agents, as well as immunotherapy and the management of advanced disease. These are my disclosures as well.

Esophagogastric cancer is not an uncommon disease in the United States. If we look at the incidences collectively, over 43,000 cases will be diagnosed in the U.S. this year; a little bit less than 3% of cancers. More distal gastric cancers continue to decrease in incidence in the United States; that's probably due to eradication of Helicobacter pylori infection as a risk factor. And

we continue to see a shift in the epidemiology to the proximal stomach and distal esophagus. And you can see that survival has improved over the last 3 decades from 5 to 15% back in the ’70s, now to 20 to 30% in the modern era. We have made modest advances in improving survival, but clearly a long way to go to improve outcomes in this disease.

This shows the staging of patients with gastric cancer. This was a large surgical database that led to revision of the AJCC staging. And this is pretty much to indicate, if you look in the left-hand panel, that once you get to T3 and T4 disease, your survival falls below 40%. Any node positivity in the center, your survival is less than 40%. And most of the patients that we see are going to be stage III disease where we see survival with surgery that’s generally less than 30 to 40%.

Esophageal cancer is even worse if we look at survival. And pretty much if you get to even T2 disease, only 40% long-term survival; T3 disease 35%; and for node-positive disease, survival with surgery alone is less than 20%. These are diseases clearly where doing something more than surgery is indicated.

How do we stage these diseases? We have to make a diagnosis, so we start usually with endoscopy, and biopsy it for tissue confirmation. We usually start with a CAT scan of the chest, abdomen, and pelvis to assess for metastatic disease, and if patients don’t have metastatic disease, we should do an endoscopic ultrasound that gives us accurate T and nodal staging. Why do endoscopic ultrasound? If you have a very early-stage tumor like T1, you could

potentially treat these endoscopically with endoscopic mucosal resection or endoscopic submucosal dissection.

For T2 tumors with negative nodes, we might consider up-front surgery but the vast majority of patients that we see are going to be T3 or node positive. If you see T3 or node-positive findings on endoscopic ultrasounds for stomach cancer, you should do a laparoscopy.

Staging laparoscopy will yield a positive cytology or peritoneal or liver findings in about 25 to 30% of patients. That's clearly going to upstage the patients. So you don't just send these patients for neoadjuvant treatment. If they have metastatic disease up front, you need to know that and then you would shift more to chemotherapy alone, the other important staging tool, and laparoscopy more for gastric than esophagus cancers. For PET scan staging, we can identify another 15% of patients that have occult metastatic disease, so a PET scan should also be considered as part of staging.

This shows an endoscopic ultrasound image, and you can see on the left it's clear that that tumor is penetrating all the layers of the esophagus and then at about 2 o'clock and 4 o'clock you can see echogenic lymph nodes. This would be a T3, N1 tumor; you can do FNA on the lymph nodes. And the staging accuracy with a combination of EUS and FNA is about 80 to 90%. To stress that for very early T-stage tumors, T1 tumors, you can consider endoscopic mucosal resection. Surgery for more advanced T1b2 tumors and neoadjuvant or combined modality therapy for T3 or node-positive disease.

This just shows the utility of PET scan. This is a patient I treated a couple of years ago. You can see a pretty massive primary tumor, but if you look, you can see a left supraclavicular lymph node. This would upstage this patient to really incurable advanced disease. This is not a patient that would benefit from combined modality therapy or surgery. And this patient, when I started him with chemotherapy, within 4 or 5 months he had diffused bone metastasis.

The other role of PET scan, which we'll talk about a little bit later, is a PET scan may be useful to assess response to preoperative chemotherapy. And here you can see in the center, a PET of a GE junction tumor, that after a few weeks of preoperative chemotherapy had a substantial response. And using PET scan can be both predictive and prognostic, and we'll talk about clinical trials that are evaluating this as a biomarker of response to preoperative treatment.

For gastric cancer, there are three accepted approaches; this is where it gets a little confusing. Pretty much chemotherapy is included in combination with surgery. The original positive study for adjuvant treatment came from the U.S. back in 2001. Patients got up-front surgery and then postoperative 5-FU radiation. For many years, postoperative 5-FU radiation after gastrectomy was the standard, but this is most appropriate in patients that really haven't had great surgery. If you have less than a D1 resection, a surgeon didn't get a lot of lymph nodes, radiation is more important.

Then, in the mid-2000s, the British reported the results for pre- and postoperative chemotherapy with ECF, so perioperative chemotherapy without radiation. And most of the patients on this trial had D1 or D2 resection; the quality

of the surgery was better. This established a standard in Europe and the U.S. for perioperative chemotherapy, and I'll talk a little bit about postoperative chemotherapy. This is done more in Asia. Routinely, patients get up-front gastrectomy with a D2 resection and adjuvant chemotherapy with capecitabine and oxaliplatin for 6 months has become the de facto standard of care in Asian countries.

Now, a little bit different for esophagus and GE junction cancers, here I think there is a clearer role for radiation. Perioperative chemotherapy does modestly improve survival, but there are problems with that approach. The most commonly used approach in the U.S. is combined chemotherapy and radiation either by itself and squamous cancers of the esophagus are followed by surgery.

This is the U.S. approach of postoperative 5-FU radiation. This has been updated a number of times, and you get about a 10% improvement in survival for adding 5-FU radiation after surgery compared to surgery alone. This is the magic approach from Great Britain where you give pre- and postoperative chemotherapy without radiation, and you can see a similar survival benefit of about 13% compared to surgery alone.

And then here are the Korean data for capecitabine and oxaliplatin, and you can see improvements in disease-free and overall survival for postoperative chemotherapy. There are three accepted approaches. I think if you do up-front surgery, you've done a D2 resection, and the patient has stage IIII disease, they should get capecitabine and oxaliplatin. If you do up-front surgery and the

surgeon only took eight or nine lymph nodes, then you might consider a postoperative 5-FU radiation.

For esophagus and GE junction cancers, here's where I draw the line. I don't think that chemotherapy alone is enough for these patients. And the positive study was the MAGIC trial; 13% improvement in survival for ECF. But look at the rates of R0 resection; there were only about 66%. And then there are larger trials of preoperative chemotherapy that actually just failed outright. It was the U.S. trial of 5 months or 5-FU platinum; it was a negative trial, R0 resection rates of only 60%. If you have an R1 resection, that means a positive margin resection, you're dead. You're essentially writing off 30 to 40% of patients with preoperative chemotherapy.

Another study that was reported as positive, I don't think was a positive trial, MRC OEO2. This treated 800 patients. They had a 5 to 6% improvement in survival, and the curative resection rates were about 60%. Recently, the British reported OEO5. This was a 900 patient study, so you could say the earlier studies, they didn't do endoscopic ultrasound, they didn't do PET scan, maybe if we stage the patients better, perioperative chemotherapy would work better. This was also a negative trial. One thing it showed was that ECX, adding epirubicin to chemotherapy, was no better. They compared ECX versus platinum 5-FU and there was no difference. In a contemporary trial using endoscopic ultrasound and PET scan staging, they still reported R0 resection rates of 60%. So, essentially, you're condemning 35 to 40% of your patients to die because they couldn't be operated on. I don't think preoperative chemotherapy is enough.

What about chemo/radiation? The standard of care really was established by a Dutch study. This was published in the *New England Journal of Medicine* back in 2012. Survival had been updated in more recent publications. But this used a modern chemotherapy regimen easy to administer, no Mediport, no infusion pumps, weekly bolus paclitaxel, weekly carboplatin for 5 weeks with concurrent radiation followed by surgery. And this was a positive study; 13% improvement in overall survival, benefits for both the squamous cancers and the adenocarcinomas. But here's the key: R0 resection rate with surgery alone is 69%, so that's what you saw with chemo alone even in the modern OEO5 trial, 900 patients. It was improved to 92% with chemo/radiation. You give your patients a better shot here. You have a better change of curative resection, and also some of the patients were pathologic complete responses; there was no cancer remaining at surgery, and nearly half of the patients with squamous cancer and a quarter of the patients with adenocarcinoma.

This has really become a global standard of care, and I've been arguing with my European colleagues, how can you give somebody chemotherapy alone to a GE junction tumor when 40% of the time you can't operative on them after you give them chemotherapy alone? What are the regimens we can combine with chemo/radiation? Carboplatin/paclitaxel is really the standard. The cooperative group ECOG did a comparative trial of paclitaxel kinesis platinum versus irinotecan kinesis platinum and saw no difference. The SWOG group used oxaliplatin and 5-FU; I think that's an acceptable alternative to carboplatin

and paclitaxel. They reported very similar results to the CROSS trial, pathologic CR of 27%, median survival of 33 months.

There was a French trial that compared in the nonoperative setting, 5-FU platinum versus FOLFOX with radiation, and saw no difference. Some of the diehards that still want to inflict very toxic 5-FU platinum on patients don't do it, give them FOLFOX rather than 5-FU platinum with radiation.

As I said earlier, we have made modest improvements in survival; 10 to 15%, that's not a homerun. Still, the vast majority of our patients, more than 50%, even when they go through neoadjuvant treatment and surgery, they're still going to succumb to their disease. What about more chemotherapy is probably not the answer? There are studies that suggest that prolonged chemotherapy, additional cycles, don't add benefits. What about targeted therapies? What about giving a targeted agent in high-risk patients to potentially suppress rather than eradicate residual disease? There's actually an ongoing study now of nivolumab. We'll talk about nivolumab later. That's an anti-PD-1 drug after chemotherapy, radiation, and surgery for esophagus and GE junction tumors, adenocarcinoma, and squamous cancer. If any residual disease is still present at surgery, they get randomized to a year of nivolumab versus placebo. Probably some of your centers are running this study. I think it's a good trial, and I encourage you to enter patients. The standard of care after this treatment is really to observe patients, and this is an innovative study and also likely to have a low rate of toxicity.

What about using PET scan to guide treatment? There were some landmark studies done in Germany that looked at PET scanning during perioperative chemotherapy. And this was a large study done in esophagus and GE junction cancers where they took 65 patients, they gave 5-FU platinum-based chemotherapy alone, but they got a PET scan a couple of weeks into the treatment, and they defined a PET response as an SUV decline of more than 35%.

The PET responders did better. If you were a PET responder a couple of weeks into treatment, you were a histopathologic response. That means some tumor regression pathologically was 44% versus 5%, and you nearly doubled the 3-year survival. PET scan does appear to be an important biomarker during preoperative chemotherapy.

The Germans then took this a step further; they did the MUNICON trial; they used the PET scan to make a decision. This was a study of esophagus and GE junction tumors, adenocarcinomas. They got a PET scan before treatment, a couple of weeks of chemotherapy, and then a repeat PET scan. If you responded, if your SUV went down more than 35%, you completed 3 months of chemotherapy. But if you were a PET nonresponder, they stopped the treatment. They said, “Why continue the treatment If you’re not benefiting?”

The PET responders did much better, the median survival actually wasn’t reached. The PET nonresponders did more poorly. You did still cure some of these patients, but they did more poorly.

Of course, then the criticism would be, “Well, they did more poorly because you stopped the chemotherapy. If you had just continued the chemotherapy, maybe they would have done better.” But that’s not the case. Here you see on the results on the right, this is the curve I showed you where if you’re a PET responder you did better, and if you were a PET nonresponder, your survival was worse. The slide on the left everybody got 3 months of chemotherapy regardless of whether or not you responded. And you can see that continuing in that red curve on the left, if you continued 3 months of chemotherapy you did not help those patients. Actually, you could argue on the right-hand curve that that purple curve, they did better if they went right to surgery rather than continuing many months of inactive treatment.

I think what we learned from this study is that PET scan is an important biomarker, a response to preoperative chemotherapy. If you don't see a response on PET scan, you might as well stop the treatment and send the patient right to surgery, or how about changing the treatment? Changing to a different chemotherapy to see if you can improve outcome? I think we learned from the German data that it’s unlikely that nonresponding patients will gain from continuing the same preoperative chemotherapy, and if you stop something that’s not working, you don’t hurt the patients.

Based on this, we designed a trial through CALGB and esophagus and GE junction cancers where we asked the question, “Can you improve outcome by changing the chemotherapy if your PET scan doesn’t show improvement?” On this trial, we took T3, 4, and node-positive patients and we assigned them to get

either chemotherapy with FOLFOX or carboplatin and paclitaxel. We got a PET scan about a month into treatment, and you can see on the top that if they responded to their regimen, if they were PET responders, then you continued that same chemotherapy during radiation. This was a sandwich approach. They got chemo up front, then chemo/radiation, then surgery.

On the top, on the right, if you're a PET responder, you would continue the same chemotherapy during radiation and then go to surgery. If you were a PET nonresponder where we know that chemotherapy is probably not working, they crossed over to the other treatment. If you got carbo/paclitaxel and it didn't work, you switched to FOLFOX during radiation. If you got FOLFOX as induction chemotherapy and it didn't work, you switched to carbo/paclitaxel during radiation.

We've completed this study, we'll be submitting an abstract to the GI Cancer Symposium upcoming in January. I can tell you that the study met the primary endpoint because normally patients that are PET nonresponders and they continue the same chemotherapy, their pathologic complete response is about 3 or 4%. We pumped it up to 18 or 19% by changing the treatment. We're very excited about this, we have to wait for more data to come out, but it does suggest that using an early PET scan to direct preoperative treatment may improve outcome in nonresponding patients.

What about new approaches? We'll talk about gemtuzumab a little bit later. This is a HER2-targeted drug and HER2-positive disease. There is a recently completed trial combining trastuzumab with chemo/radiation in

esophagus and GE junction cancers. This is RTOG 1010. Patients had to be HER2 positive; they got randomized to standard chemo/radiation followed by surgery versus chemo/radiation plus trastuzumab followed by a year of trastuzumab after surgery. This trial has been completed; overall survival is the primary endpoint, and hopefully we'll be hearing results from this sometime in the next year.

STEVE Like Sandy said, my name is Steve Malangone and I'm a nurse practitioner at the University of Arizona Cancer Center.

Gastric and esophageal cancer is a beast, and in preparing for this talk, coming out here, I had an opportunity to go for a run yesterday morning; more of a stumble than a run, I'm not a runner. But if any of you had a chance to go down to the waterfront and saw this picture, I saw this guy and I thought about all the data. What we just heard is just localized disease; we haven't even talked about metastatic disease yet. And for a solid tumor of the GI tract, this is a very complicated disease to treat.

I saw this guy and I'm not an art person, but I thought, "Man, that's me," That's all of us when we're involved in treating patients with this disease. And then you see how nicely raked that all is early in the morning? I wasn't sure -- it looked like a zen garden -- if I was allowed to, but I went down there and I got a really close look at this guy and I thought, "Man, that's really narcissistic of me. This isn't me. This is somebody with a GI cancer of the upper GI tract, specifically, a GE junction tumor." How many of you guys take care of these patients? You guys are the go-getters of the go-getters, so you're not here to talk

about public art. But the reason I included this is because when we treat these patients, how many of you guys number your plans when you write a progress note? You use numbers. And then how many people just put a pound sign on the plan?

People who put a pound sign when they treat these patients are more relieved because when you number, you're usually in the double digits. They're very complex patients and so the real question is, "How can we help these patients?" For the first case, this gentleman is a 53-year-old man. He presented to his primary care provider, he had 6 months of worsening dysphagia and 20 pounds of unintentional weight loss. Why did he wait 6 months? Because he's a 53-year-old man. He had an EGD and it showed this mass that you see up on the screen at the GE junction, causing stenosis of the distal esophagus, extending into the cardia fundus and proximal gastric body. This is at least a very locally advanced GE junction cancer. Biopsy showed adenocarcinoma, and he was referred to us at that time.

At his initial evaluation, he had dysphagia to solid foods and some liquids with painful swallowing, but he was still taking nutrition by mouth. He had 20 pounds of weight loss. He denied anything that would indicate that he had frank blood loss from the GI tract, including hematemesis, hematochezia, melena. He was otherwise asymptomatic. He remained active, working as a police officer. On physical exam, it was basically negative. He might have had a little tenderness in the epigastrium. His CBC showed that he had low-grade anemia, maybe he lost it from the GI tract, maybe this was nutritional. And then he had serum chemistry,

which showed essentially normal renal and hepatic function, which is good, which means we can probably treat him. And his albumin was a little decreased at 3.1, probably related to nutrition.

We should talk about dysphagia a little bit because that's something that we really need to take into consideration in management of both metastatic and locally advanced disease. Patients with dysphagia who have locally advanced disease, we really have to think about supporting the nutrition. Because what happens after you start radiating somebody who has a locally advanced tumor? Sometimes it actually becomes edematous, and then they become obstructed, and they end up in the hospital when they can't drink. We give them hydration in the clinic as much as we can, but ultimately we need to be thinking ahead in that area.

For nutritional reasons, we oftentimes put an enterostomy tube, and when it's somebody who's a surgical candidate, it should be a J-tube for technical reasons that deal with the surgery that we're planning. When patients have metastatic disease, I've actually found often this is the biggest quality of life issue. It's not the pain, it's not the bleeding, it's not side effects from chemotherapy, it's actually not being able to eat. So it's really important that we're addressing their nutrition in other ways.

In the metastatic setting, sometimes it's better to try to do something palliatively, whether it's radiation, stenting, dilation. Those things are all considered, and it's important to have access to a gastroenterologist who can see your patients quickly who is expert in those procedures. For staging, we use

PET CT, and this is what his PET CT showed. He had at least this locally advanced tumor. There was no evidence of distant metastasis.

We also sent him to our gastroenterology clinic, and he had an endoscopic ultrasound to complete his staging. This is what the EUS showed -- these are the actual images, and he had at least one lymph node. EUS is nice, it can better assess the depth of invasion, and that's why we choose it when we can. The ultrasound is able to tell us how deep the tumor has gone into the muscularis or whether it's penetrated through. So this is a very high-risk disease.

If you remember the chart that Dr. Ilson had early on, these patients are very unlikely to achieve a cure, but without metastatic disease we started. There was an FNA done at the lymph node. Why the lymph node and not the primary tumor? If you can prove that the lymph node has cancer in it, then it's actually proven lymph node–positive disease. He also had an EGD in the community before that biopsy in the primary tumor, so you don't have the risk of having no path in that situation.

We refer our patients up front, and it's recommended to nutrition, radiation oncology, and thoracic surgery. The plan to put a J-tube in these patients who are being set up for neoadjuvant therapy followed by resection, trimodality therapy should be discussed carefully. A lot of patients don't have much dysphagia, but if the degree of obstruction is relatively high, if you can't see a very big space for the food to move through, sometimes the radiation oncologist or the surgeon will recommend that we go ahead and place a tube. He did have a J-tube placed, and we discussed his case in our tumor conference and we

discussed giving him treatment according to the CROSS regimen with an overall plan for trimodality treatment for a very fit patient.

He had weekly visits with us. He was treated with carbo/paclitaxel. He tolerated well overall during the first 3, 4 weeks, which is common, and then at the last couple of weeks, it's sort of a crescendo fatigue and he also developed esophagitis dysphagia at that time. On week 4, he came in 10 pounds of weight loss, he was a little hypotensive, a little tachycardic. For a fit person, this means he's probably very dehydrated and very malnourished. His albumin had dropped at that point. We provided IV hydration in the clinic and we treated him empirically for esophagitis, so something to block acid and something to block with the pain because he was actually having kind of a substernal type pain. We planned to refer him back for an EGD if necessary, which we didn't have to do. He met with nutrition and started enteral feeding that day.

He went on; he completed the rest of his treatment. This was our PET scan following treatment; he had a very good radiologic response. And then the outcome; he went on to have esophagectomy 8 weeks after completion of treatment, [and] the final surgical path showed adenocarcinoma. He was downstaged from a T4 N1 to a T1 N0, and there is good data to say that the prognosis for people is associated with the degree of downstaging. He does have a fairly good prognosis as compared to where he was at the start. And he's followed now in our survivorship clinic.

DR. ILSON A couple of comments on the excellent case. In the setting of metastatic disease, which we'll talk about now, dysphagia can be improved with

chemotherapy alone, so we don't always have to rush to put stents and feeding tubes in patients.

If you look at the clinical data for even some randomized trials, you get dysphagia relief of about 70, 80%. So as long as patients are getting in liquids and they can hydrate themselves, we'll start with chemotherapy first and then do the other interventions later. And just a little scolding about your surgeon, to take only nine lymph nodes. I know sometimes it's harder to find lymph nodes after chemo or radiation, but the accepted minimum is 15.

What about metastatic disease? This is going to affect 40% of patients at diagnosis. And unfortunately more than 50% of patients that we treat with curative intent will develop metastatic disease. So, unfortunately, the vast majority of patients are going to wind up receiving palliative chemotherapy for esophagogastric cancer.

There have been randomized trials; they're small, but randomized trials comparing best supportive care versus chemotherapy. And this is one of those infamous forest plots so that anything to the left of the midline means you do better with the intervention, anything to the right means you do worse. You can see that chemotherapy is probably better than best supportive care. You get modest improvements in survival with active chemotherapy.

Rather than go through the litany of all the regimens and all the trials, I like to show this slide because it really tells us that everything's the same. It doesn't really matter what chemotherapy regimen you pick, the industry standards are on the right; DCF and ECF, I'm not a fan of either of these regimens because they're

more toxic, they're triplet regimens. The regimens in the middle, like capecitabine, cisplatin, FLO, FOLFOX, FOLFIRI, if you look across the board, the response rates are the same; they're 40%. The time to progression is the same; it's 5 to 6 months. And the median survival, which is not very good, is about 9 to 10 months. That's kind of the state of the art of chemotherapy and, generally, two-drug regimens are better, usually a 5-FU drug and a platinum agent. We typically use FOLFOX now as the standard regimen or capecitabine/oxaliplatin. Adding third drugs we'll talk about, but in most patients, two-drug therapy is the preferred palliative regimen.

How do we select patients for chemotherapy? We have to look at age and functional status and comorbidities. I know there's a lot of talk about biologic versus actual numeric age, but there are clear data that older patients don't tolerate treatment as well. You're not going to give DCF to a 75-year-old with metastatic gastric cancer, and there are actually studies to suggest that you don't get a benefit from these more toxic regimens in older patients.

But combination chemotherapy is clearly preferred over single agents. We're going to reserve single-agent chemotherapy for the elderly with really poor functional status. On the other extreme, the three-drug regimens, DCF or modified DCF, or FLOT, which is the German version of this, we're going to reserve for high functional status in younger patients without comorbidities. They certainly have to know what they're getting themselves into. You add a taxane to treatment and you add alopecia and fatigue and myelosuppression, and oftentimes even with modified schedules of these triplet regimens, these patients

are spending their 2 weeks between treatment recovering from side effects, so it's an informed decision as well. And if you're going to give these patients more toxic therapy, you need to follow them up more carefully and they have to get frequent toxicity assessment.

Oxaliplatin is taking over cisplatin as the preferred regimen. This is a head-to-head German study where they compared 5-FU oxaliplatin versus 5-FU cisplatin, and you can see, the 5-FU/oxaliplatin regimen trended better; better time to progression and a better response rate, so clearly oxaliplatin was not inferior in this German trial.

But if we look at age, if you're over the age of 65, the cisplatin curve is yellow and the oxaliplatin curve is blue. If you're over the age of 65, you should get 5-FU/oxaliplatin. You do better, you even have better survival and progression-free survival. 5-FU/oxaliplatin in most patients would be preferred over cisplatin, unless there are reasons not to give oxaliplatin; if they have severe neuropathy, you might consider low-dose cisplatin.

What about other trials? This is the ECF trial from Britain. This was 1,000 patients. You can see survival was equivalent whether patients got cisplatin or oxaliplatin and if they got IV 5-FU versus oral 5-FU. I tend to prefer infusional 5-FU because capecitabine has very significant cumulative skin toxicities. These patients get really severe hand-foot syndrome if they're on this drug for a long period of time. Even though capecitabine and infusional 5-FU are equivalent, I really prefer to give my patients infusional 5-FU. Here is Asian data showing that capecitabine is equivalent to IV 5-FU in progression-free and overall survival.

What about DCF? Some of my colleagues still give this treatment to most of their patients. This is the randomized trial that compared cisplatin/5-FU versus adding a taxane. However, both of the regimens were pretty nasty here because they used high-dose cisplatin with a 5-day infusion of 5-FU, which nobody should do anymore. You should do FOLFOX or 2 days every 2 weeks. They compared the worse control arm, the most toxic control arm, with the addition of a taxane on top of it, and you did get a survival benefit. You did get a modest survival benefit; median survival was improved by about 2 months. And overall survival also was improved for DCF versus CF.

The problem, however, is this is pretty toxic. You had fairly significant rates of grade III and IV diarrhea, stomatitis, nausea/vomiting, neutropenia 82%, 30% had neutropenic fever, and to me this is telling. If you look at the bottom 49% of patients on DCF came off for an adverse event or they just said, “Stop this treatment.” They didn’t come off because they were progressing, they came off because it was too toxic.

The other thing, I reviewed these publications when they were submitted; the median age of patients on this trial is 55. So this is not your typical 70-year-old lady coming into your office with gastric cancer; these were marathon runners and they still had pretty significant toxicities.

My colleague, Manish Shah, did a modification of DCF, they scheduled this like FOLFOX 2-day infusion of 5-FU every 2 weeks with lower doses of platinum and docetaxel, and if you compared modified DCF versus parent DCF, you didn’t lose anything by modifying DCF. Similar response rates -- 49 versus

33% -- the overall survivals were just unbelievable here, but this a randomized phase II trial with very small patient numbers. But you still had pretty high rates of grade III/IV neutropenia with modified DCF 56%, and a hospital stay was required in one out of five patients, so a little bit better in terms of toxicity. But this is still a spicy cocktail that I don't think most patients in our practice should be exposed to.

Again, the age issue. The Germans did a trial called FLOT 65. They looked only at patients 65 or older and they randomized patients to get 5-FU/oxaliplatin with or without the addition of a taxane in older patients. The response rate was better for FLOT; 49 versus 28%. But progression-free and overall survival was not significantly better, and you had a lot more toxicity with FLOT and worse quality of life. Patients felt worse on FLOT than FOLFOX. If you're going to live for a year or a year and a half with metastatic disease, you do not want to have worse quality of life from your chemotherapy.

And here on the top panel you can see that there was really no difference in progression-free and overall survival, with the exception of local disease, so if you're 65 and older you should not get triplet chemotherapy. If you're under the age of 60, you probably still shouldn't get it, but don't give it to older patients; it does not help them, it worsens their quality of life, and that's the name of the game in metastatic disease.

This is another area that I kind of preach about. Many of my colleagues in the community still give patients epirubicin. They give them ECF or EOF or EOX. Epirubicin does not add anything; please stop giving this to your patients. This is

a randomized trial from France. This trial did not get enough play when it was published, but this was FOLFIRI versus ECX. French oncologists are some of the best in the world. I was just at a meeting in the South of France; they do world-class research. They're the ones that developed FOLFOX and FOLFIRI. And here they randomized patients with esophagogastric cancer to get FOLFIRI versus ECX -- 416 patients. You can see there was no difference in outcome. The response rates were the same, progression-free survival was the same, overall survival was the same; however, if you look at the graph on the right, the primary endpoint was time to treatment failure. Time to treatment failure also incorporates toxicity; time to progression purely looks at progression. If you look at time to treatment failure, you include patients that came off because they couldn't tolerate it, and FOLFIRI was better. FOLFIRI is the blue line and ECX is the yellow line.

If you're working with your practitioners in clinic, tell them Dr. Ilson said you should not give patients epirubicin anymore; you make their hair fall out, you give them heart toxicity, and nausea and mouth sores and myelosuppression, and it adds no benefit.

What about second-line chemotherapy? Second-line chemotherapy now has a proven role to modestly improve survival compared to supportive care alone. These are two of the randomized trials on the right. This is docetaxel versus best supportive care. You can see a survival better. And on the left, patients could get either docetaxel or irinotecan versus best supportive care.

When patients fail FOLFOX, we can consider a taxane or irinotecan as a standard second-line chemotherapy.

The New Yorker always inspires me; every time I open it every week I always find these cartoons and I think this sort of summarizes what I do for a living as a medical oncologist. And you can see this ship is sailing along nicely on first-line chemotherapy and then it hits the iceberg and then patients get on the lifeboat and they do okay for a while and then they hit another iceberg, second-line, then they get on another lifeboat and you can see that lifeboat is getting smaller and more crowded, and there's another iceberg coming up in the future for them.

The real focus now in new drug development is targeted therapies. I showed you data that conventional chemotherapy really is modestly effective; about 40% of patients respond. Median survival is less than a year; second-line chemotherapy may be about 10% of patients respond with a median survival of 6 months. Conventional cytotoxic chemotherapy has limited benefits, so why targeted agents? Because we're really tending to block more specific tumor growth factor pathways, monoclonal antibodies, tyrosine kinase inhibitors, soluble receptors to growth factors, and also trying to inhibit the downstream pathways from these membrane-based receptors growth pathways.

What about genomic profiling of gastric cancer? How should we do this and what methodology? First of all, let me preface these comments that although everybody wants their gene profiled and some cancer centers say, "We're going to find the magic cure for you if we do profiling." -- that, unfortunately, is not the

case. 95%+ of the time, genomic profiling finds no useful information. I know it makes nice TV ads and it looks very promising and you see the key going into the lock, but, unfortunately, 95%+ of the time genomic profiling -- we find you have a P53 mutation, congratulations, it doesn't help you.

How can we profile tumors? We still do protein expression by IHC; that's how we determine HER2 positivity. If the immunohistochemistry is equivocal, we do FISH testing. Gene expression by MRNA still hasn't really caught on. DNA array -- I don't know if Dr. Hamlin talked about lymphoma, and DNA array screening can prognosticate in lymphoma. This has not been too helpful in other cancers because it looks at thousands of genes, and you get these green and these red plots that show that a thousand genes are affected in this cancer and that cancer -- not helpful yet in esophagogastric cancer.

Whole exome sequencing, that's what Foundation Medicine and companies do. And the utility of this testing, it still is a research test looking for more specific mutation, amplification, and promoter hypermethylation. And then regulatory RNAs, those are the small RNAs; a very interesting area of research, but not yet any clinical application.

The Genome Atlas Project being headed by Adam Bass at the Dana-Farber looked at 300 fresh frozen gastric and GE injunction adenocarcinomas. They looked at six platforms to profile these tumors genomically. So one of their earlier publications, in the first 150 tumors, they found 26 significant genes with mutation or genomic loss. The targetable ones include cyclin-dependent kinase and PI3-kinase; those are activating mutations, so they become super activated

proteins, but no drugs yet. Then a number of tumor suppressor genes; SMAD4, ARID1A, and p53, which is mutated about 50 to 80% of the time, not targetable. But unlike other cancers, 50% of colon cancers have Ras mutations, less than 5% of esophagogastric cancers have Ras mutations. Also, rare BRAF and EGFR mutations, these are important mutations in colon and non–small cell lung cancer, but they're rarely affected in esophagogastric cancer.

What about gene amplification? Here are data from the whole 300 tumors and what is clear is if you look at the graphic on the right, the blue bars are colon cancer and the red and orange/yellow bars are esophagogastric cancer, and you can see that gene amplification is a lot more common in esophagogastric cancer than colon cancer. These are probably genomically more complicated tumors. 37% of GE junction gastroesophageal tumors have amplification of one of these five pathways. Four of them are targetable: EGFR, HER2, MET, FGF, so these are targetable pathways. The problem is, however, as I said earlier, we love to do genomic profiling, but it doesn't always result in success. The studies that have tried to target EGFR have universally failed; cetuximab, panitumumab, erlotinib have not improved outcome added to treatment. HER2, the results are mixed, we'll talk about it. MET, a large, randomized phase III trial even in biomarker selected patients with MET overexpression, adding a MET inhibitor did not improve outcome. FGF is ongoing.

From the Genome Atlas data, the other interesting thing is that there are four genomic subsets of upper GI cancers. 50% of gastric cancers are what we call "genomically instable tumors;" they have high rates of p53 mutation, and

these are the tumors that have the amplification of the receptor tyrosine kinase pathways; so these are the HER2-positive patients, the patients with EGFR, FGF amplification. If you look more specifically at the GE junction subset, it's 90% are chromosomally genomically unstable.

A second smaller group has a high rate of gene mutation and maybe a higher rate of microsatellite instability. Another group, 20%, this corresponds to the diffuse gastric cancers. They are pretty genomically bland. We could only find CDH1 and role mutations, not a lot of mutations. And then another small subgroup, about 9% of gastric cancers have associated infection with Epstein-Barr virus infection. These are the ones with the high rates of PI3-kinase mutation, which is potentially targetable, and they also appear to be immune driven. High rates of PD-L1, PD-L2 amplification may be a subset that might benefit from immunotherapy.

Here we see the subsets geographically, chromosomally unstable tumors largely in the GE junction, and then the other subsets EBV, MSI, and genomically stable, are present more in the distal stomach.

Here it shows that if you're going to try and target a subgroup for immunotherapy, if you look higher up in the curve here represents the higher expression of PD-L1, PD-L2 and you can see that the EBV and the MSI subtypes are the ones that have the highest expression of these immune-inhibiting ligands, and we know that PD-L1 may be a surrogate biomarker for benefits for immunotherapy.

What about HER2? This is the one success story. The trial that showed a benefit for trastuzumab was the ToGA trial, but look how ambitious this trial was. They screened nearly 4,000 patients to identify about 580 that actually went on trial and they were randomized to capecitabine platinum with or without trastuzumab. You did get survival benefits, so this trial led to the approval of trastuzumab in HER2-positive GE junction and gastric cancers. And if you had high expression, these are really the only patients that we treat. You have to have either a high 2+, FISH+, or IHC 3+. Here, you get nearly a 5-month improvement in survival, so high expressors benefit from the addition of trastuzumab to chemotherapy in metastatic disease.

However, remember I told you earlier the results with HER2 are mixed? Lapatinib, this is the HER2 tyrosine kinase inhibitor we studied in the LOGiC trial. Patients got CapOx with or without lapatinib. This is the infamous banana curve; it looks like it works initially, but it didn't in the long term, so lapatinib failed to improve outcome when added to chemotherapy.

What about ongoing HER2 trials? In first line you've got JACOB. We do have evidence from breast cancer that if you -- pertuzumab targets HER2 and HER3. In breast cancer, dual-targeted HER2 therapy is better, so breast cancer patients up front will get pertuzumab and trastuzumab plus chemotherapy, so the trial in gastric cancer has been completed; cape/cis trastuzumab with or without pertuzumab 780 patients. One caveat here, they have yet to present the data. This was going to be presented at the ESMO meeting a few weeks ago and they

pulled it. It's never a good sign when somebody pulls a presentation of a trial at the last minute.

Second-line GATSBY -- this was paclitaxel versus T-DM1. T-DM1 is improved in breast cancer, it's effective in second-line HER2-positive breast cancer; however, in gastric cancer, T-DM1 failed to be any better than paclitaxel by itself.

Except for HER2, there's no identified biomarker for gastric cancer, and recent trials in EGFR and VEGF inhibitors largely failed. However, we do have positive results now for ramucirumab in second-line treatment. These are results of the REGARD trial. This took patients failing 5-FU platinum and randomized them to get best supportive care or best supportive care plus ramucirumab. And you can see modest improvements overall in progression-free survival; this led to FDA approval for this drug in second line.

Remember I showed you the curves earlier of docetaxel and irinotecan versus best supportive care? If you look at ramucirumab on the top versus best supportive care, it looks a lot like second-line chemotherapy. So there is an argument in patients that might not tolerate second-line chemotherapy to give ramucirumab alone.

But I think the most clinically relevant second-line trial is the RAINBOW trial. This took patients failing 5-FU platinum, they were randomized to get paclitaxel alone versus paclitaxel plus ramucirumab, and here you got a survival benefit of 2.3 months. And this set a new benchmark; nearly a 10-month survival in second-line treatment for paclitaxel ramucirumab improvements in

progression-free survival, as well as response rates. This is now the de facto second-line standard of care, paclitaxel plus ramucirumab.

There is an ongoing randomized trial in first-line disease; capecitabine, 5-FU plus platinum with or without ramucirumab. This trial has been completed and I'm going to an investigator meeting in a couple of weeks in Germany to get an update whether this trial will yield a positive result.

Then, lastly, I'm going to talk briefly about immunotherapy. The drugs that we are using target either the CTLA4 or PD-1 pathways. PD-1, you activate the death receptor and you kill off T cells. If you block the pathway, you get a blossoming of an immune response. CTLA4 shuts down T cells as well. If you block the pathway, you get a burst of immune response.

If we look at the -- higher up on the right means the mutations you have in your cancer. The more mutations you have in your cancer, the more likely you're going to activate the immune system. And you can see that stomach and esophagus cancer are actually higher up on the spectrum, so these are diseases that are potentially candidates to treat metastatic disease, and I showed you this earlier.

Here's a snapshot. I'm not going to go through all the studies, but we do see single-agent activity for both pembrolizumab and nivolumab of about 10 to 20% response rates. Also, PD-L1 drugs, like durvalumab and nivolumab, have activity. And in combination therapy, ipi/nivo is now going to go to a phase III comparison of chemotherapy. These are the ongoing pivotal trials. I told you about the nivolumab trial. First-line pembro is being compared to chemotherapy,

second-line pembro versus paclitaxel. And modulation agents, like IDO inhibitors and co-stimulatory pathways are under investigation.

Now we're going to shift to a case presentation.

STEVE I'll try to be very brief here. Basically, this is an ECOG 0; 66-year-old woman who presented to her PCP with iron deficiency anemia, she reported 30 pounds of weight loss, said she was on a diet. How many times have we heard that? If you ever go on a diet and then you successfully lose weight, it will terrify you if you work in oncology because too often it's actually the first sign of a cancer that's there that they just don't have any other symptom of yet.

that was her story. I'll just leave some of this for you to read. Briefly, this was her PET CT, what stage is this?

AUDIENCE Four.

STEVE Good, everybody's still awake. We met with her, we talked to her about starting FOLFOX right away, we sent her tissue for HER2. At that time, she actually had normal renal and hepatic function by her first follow-up; her AST, ALT, and bilirubin were starting to rise. While the bilirubin was still normal, it was a significant upward trend, so we knew we had a very limited window. And oftentimes in GI solid tumors we don't actually get to turn the corner in this kind of situation.

This is really a two-part story, so part one is kind of grim. She got one dose of FOLFOX and ended up in the hospital with neutropenic fevers. I'll let you read the slide on your own. She came to see us in follow-up and was ready to quit. Her HER2 testing came back IHC 2+ and FISH was positive. We had extra

time to run that since she was hospitalized, and we added trastuzumab to her treatment plan. We also added pegfilgrastim since she had neutropenic fevers.

I had intended to talk a little about bleeding. The bottom line in her case is we chose to start her on chemo right away because her most significant symptom was that she was headed towards hepatic failure. But in some patients who have bleeding who don't respond to chemotherapy, we radiate. [Radiation is] probably the best way to go, and there are also other endoscopic interventions; if that fails, they can be coiled, so bleeding is important to address.

As far as the outcomes are concerned, I'll go right to the PET CT; I'll let you read that on your own. This was before and then this is after. I think it's important that we find some satisfaction in our work and that we help people. And I like to go back and forth sometimes on this when I feel sad.

She did progress after a year, and she still was of high performance status. So she started second-line treatment with paclitaxel and ramucirumab, and there was no more bleeding at that point because ramucirumab's a VEGF agent. She did develop hypertension after 3 months; we started amlodipine. It's less common than with other VEGF agents, but we do see it. And proteinuria, but the 24-hour urine was less than the 3 gm, so we continued. She didn't progress after 9 months. We did molecular sequencing and she's being considered for a phase I trial looking at immunotherapy.

DR ILSON A comment about economics; when a patient has obvious metastatic disease, don't get a PET scan. It's much, much more expensive and I know the pictures are really pretty, but it's much more expensive and most

patients you can probably get by with a CAT scan to image obvious metastatic disease. And actually sometimes the PET scan overstates things. The PET scan looks so dramatically better and it's a complete response; that doesn't mean it's a complete response. I would use PET scans sparingly. If the CAT scan doesn't visualize the disease well, you should get a PET scan, but in most patients, stick to CAT scans; you'll save thousands and thousands and thousands of dollars and your insurance company will like you better.

[END]