

The Current and Future Management of Gastric Cancer With David H. Ilson, MD, PhD

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AJMC®: What is the burden of gastric cancer in the United States? How does it differ from the burden of gastric cancer in other countries? How has treatment changed over time?

DR ILSON: This is actually a disease that has decreased in incidence in the last century. One hundred years ago, gastric cancer was one of the leading causes of cancer in the United States. And over the last century, it has continued to decline in incidence, probably due to better food storage conditions. We used to have salted and smoked foods. Now, we have better refrigeration and better food handling. Also, there has been a decline in the population incidence rate of *Helicobacter pylori* infection. *H. pylori* infection is probably the leading cause of gastric cancer globally, and that has decreased in incidence in the United States.

I think those factors have led to a fairly dramatic drop in incidence of gastric cancer. Despite this, gastric cancer is still not an uncommon disease. We see about 24,000 Americans a year that develop this cancer, and then if we factor in esophageal cancer, which is right next door and accounts for 17,000 cases, we are talking about more than 40,000 combined cases of gastric cancer and esophageal cancer in the United States each year. But individually, gastric cancer occurs with an incidence less than 10% to 15% of the incidence seen with more common cancers we screen for, so there is no effective screening for this disease in the United States. That is in comparison to East Asia, where it is one of the most common cancers, certainly in Korea and Japan. Because it is a leading cause of cancer-related death, they have screening programs in Japan and Korea that probably lead to earlier detection in comparison to the West, where patients usually present with symptomatic disease. As a result, there is no effective screening in the United States. Gastric cancer is a disease that is decreasing in incidence, and so, as a consequence [of less awareness and less screening], most patients present with locally advanced disease and up to 30% to 40% of patients present with metastatic disease even at diagnosis.

AJMC®: Treatment is generally surgical, followed by chemotherapy in many cases. However, there remains some nonstandardization of care and uncertainties among clinicians in appropriate chemotherapeutic regimen selection. Can you discuss the lack of standardization of care in gastric cancer?

DR ILSON: Yes, I think it is becoming more standardized. Standard staging would be endoscopy, computer-aided tomography scan imaging, and then laparoscopic staging to rule out metastatic disease.

Patients who have early-stage disease—stage I—would be candidates for primary endoscopic surgery or upfront surgery alone. In patients who have stage II or III disease, we typically consider perioperative chemotherapy, which involves administering chemotherapy before and after surgery. That has become a standard since the mid-2000s based on data from the United Kingdom—the MAGIC trial—that shows that perioperative chemotherapy improves survival by about 14% to 15% and reduces the risk of recurrence by 30%.

In Asia, culturally, they prefer to do surgery up front and then give adjuvant chemotherapy for 6 months to a year. In Japan, they give a year of S1, which is an oral 5-fluorouracil equivalent. In Korea, they showed that 6 months of capecitabine and oxaliplatin also conveyed survival benefits. And, considering all these approaches, adding chemotherapy to surgery improves survival outcomes by about 10% to 15%, which translates into about a 30% reduction in the risk of recurrence.

In Europe and the United States in academic centers, we would do perioperative chemotherapy. The old standard used to be ECF (epirubicin combined with cisplatin and infused 5-fluorouracil), with substitution of oxaliplatin for cisplatin or capecitabine for 5-fluorouracil in some cases. Recent studies have suggested that epirubicin may not add a benefit to chemotherapy. And there is going to be a major presentation at the American Society of Clinical Oncology (ASCO) meeting [of a study] that looked at 5-fluorouracil and oxaliplatin with Taxotere (docetaxel) that might have resulted in better survival than ECF perioperatively, so it is possible that a taxane triplet regimen may become the new standard of care once the data are presented at ASCO.

I think there is a consensus that patients should get surgery and should get preoperative and postoperative chemotherapy, or adjuvant chemotherapy, if they have had good surgery. There is increasing controversy about whether or not postoperative radiation adds any benefit. There was a trial in Korea where they randomized patients after surgery to get chemotherapy alone or chemotherapy sandwiched with radiation, and there was no survival benefit for adding radiation. This was a trial of 500 to 600 patients.

And then there was a recent European study called the CRITICS trial, which has not been published yet, but that also looked at adding adjuvant radiation after gastrectomy. All the patients received perioperative chemotherapy, like the European and US [approaches]—preoperative and postoperative chemotherapy around surgery—and then patients were randomized to get or not get the addition of postoperative radiation. That trial also showed no survival benefit for adding radiation.

For gastric cancer, perioperative chemotherapy or adjuvant chemotherapy are standards, and it is not clear whether adjuvant radiation adds any benefits. The current research

questions are looking at new drugs, so there are trials looking at adding trastuzumab to perioperative chemotherapy. There is also a trial in Europe looking at dual *HER2*-targeted therapy combining pertuzumab with trastuzumab and perioperative chemotherapy. There is also going to be a trial opening within the next year looking at immunotherapy added to perioperative chemotherapy with anti-PD1 therapy with pembrolizumab. That trial is in development.

That is where we are right now. I think the focus on drug development right now is *HER2*-targeted agents and immunotherapy drugs, but there are no data to report yet.

AJMC®: As far as targeted therapy in gastric cancer, what are some of the trends toward moving targeted therapy into earlier treatment? How are those results likely to affect the standard of care?

DR ILSON: Targeted therapies have only been shown to be beneficial in advanced stage IV metastatic disease, and the validated target is *HER2*. Trastuzumab is active combined with chemotherapy in patients with *HER2*-positive metastatic disease. In second-line treatment, we have validation of vascular endothelial growth factor (*VEGF*)-targeted therapy. The drug ramucirumab, by itself and added to chemotherapy, is approved as second-line treatment in metastatic gastric cancer. Those are really the only 2 approved targeted therapies in the West.

There is another drug called imatinib, which is a *VEGF* tyrosine kinase inhibitor that is active in third-line treatment and was approved in China. This is now being studied in the West. And the other tyrosine kinase inhibitor that is being studied in late-line treatment is regorafenib, and that treatment is being compared to best supportive care in refractory disease.

A number of targeted therapies have failed, including epidermal growth factor receptor–targeted drugs such as cetuximab and panitumumab, both of which failed when added to chemotherapy. There was no improvement in outcome compared to chemotherapy alone. And drugs targeting the mesenchymal epithelial transition (*MET*) factor pathway also failed in phase 3 trials. Added to chemotherapy, medications targeting *MET* did not improve outcomes compared with chemotherapy alone.

I think the focus of research is new *HER2*-targeted drugs and looking at immune checkpoint inhibitors. Something that was just published—our data for nivolumab, which is an anti-PD1 drug, in chemotherapy-refractory gastric cancer for a third-line treatment—has shown interesting results. Patients failing at chemotherapy were randomized to supportive care versus nivolumab. That trial yielded a survival benefit and about a 10% response rate. Progression-free survival was improved from 11% to 27% at 1 year. As a result of this trial, we can now add immunotherapy as a potentially validated target in late-line disease. »

And we are awaiting a number of studies that are looking at immunotherapy agents now moved into earlier-line treatments. We have talked about combining pembrolizumab with perioperative chemotherapy in the new adjuvant setting. That is a trial that will be underway within the next year. I think the targets that are validated now are *HER2*, *VEGF*, and now, immune-checkpoint inhibitor therapy. Moving forward, I think we are going to see trials moving checkpoint inhibitors to earlier-line treatment, potentially in the adjuvant setting. The *HER2*-targeted drugs are already being studied in adjuvant or perioperative settings, and we are awaiting data for ramucirumab. It was approved for second-line treatment. There will be data presented within the next 6 months to a year [on] first-line ramucirumab about whether first-line ramucirumab improves outcomes when added to first-line chemotherapy. I think if this trial is positive, then there will be a revived interest in looking at ramucirumab in combination with adjuvant treatments.

That being said, bevacizumab was one of the targeted drugs that failed first-line—we talked about cetuximab, panitumumab, and targeted agents that all failed when added to chemotherapy—bevacizumab also failed to improve

survival in first-line chemotherapy. There was also a recently reported adjuvant trial adding bevacizumab to perioperative chemotherapy that also failed to improve survival compared to adjuvant chemotherapy alone. So, there are some negative trials or ongoing studies. But I think *HER2*, *VEGF*, and the immune checkpoint inhibitor pathways are the most promising, and we have positive data in earlier- and later-line treatment, and we await results for these drugs in first-line therapy. Of course, the adjuvant studies are just getting underway, but there is a clear rationale, once these drugs are validated in

metastatic disease, to move them forward in the adjuvant setting.

AJMC®: In terms of issues with standardization of care, a paper by Hess et al discussed second-line chemotherapy treatment options for advanced gastric cancer. Approximately 20% of patients received single-agent fluoropyrimidine treatment, with other standard options accounting for approximately one-third of regimens and a variety of other regimens accounting for more than half of treatments. As far as second-line chemotherapy treatments, is this result a consequence of tailoring treatment to specific patients, a result of looking at 2-drug combinations versus 3-drug combinations, or another trend entirely?

DR ILSON: I think the treatment paradigm is pretty clear. In first-line chemotherapy, we give patients 5-fluorouracil and platinum-based treatment. After that, it is arguable whether you should add a taxane up front. It is usually 5-fluorouracil and platinum-based treatment with or without a taxane. Now that we have ramucirumab in the second-line setting, which we usually combine with a taxane (paclitaxel), most of us will not give the taxane up front. We will use fluoropyrimidine and platinum-based chemotherapy first-line, and then when patients progress, the standard of care is pretty clear now: it is paclitaxel plus ramucirumab second-line. And then, third-line, if patients are well enough, we usually use irinotecan-based treatment.

The hierarchy of treatments is fairly standard. If patients are *HER2*-positive, they would get trastuzumab first-line with chemotherapy. Notably, second-line *HER2*-targeted therapies actually failed in a recent published trial evaluating trastuzumab emtansine (T-DM1) that was evaluated in the second-line setting in *HER2*-positive patients failing prior trastuzumab-based treatment. Investigators compared T-DM1 to paclitaxel, and there was no difference. Second-line *HER2*-targeted therapy with T-DM1 was no better than chemotherapy alone. It remains that we only have 1 validated *HER2*-targeted drug, and that is trastuzumab in combination with first-line chemotherapy.

We are waiting for the day when we can combine pertuzumab with trastuzumab first-line. To review, first-line treatment is 5-fluorouracil plus platinum, with or without trastuzumab. Second-line treatment would [be] paclitaxel plus ramucirumab. Third-line treatment would be irinotecan-

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based treatment if patients are well enough to get third-line treatment. And we now have an indication that nivolumab may be active in late-line treatment—certainly better than supportive care—with enhancements in response and survival for this drug with very acceptable toxicity.

AJMC®: In second-line treatment, you emphasized the importance of taxanes in combination with ramucirumab. Can you comment on possible use of taxanes in earlier therapy?

DR ILSON: I think those regimens are much, much more toxic—particularly regimens like docetaxel, cisplatin, and 5-fluorouracil (DCF), or modified DCF. They are pretty toxic, and we generally reserve those treatments for young patients with good functional status [who] can potentially tolerate higher degrees of toxicity. We might also use these more aggressive regimens up front in patients who are more symptomatic, where you need the little bit of a higher response rate. Lastly, we might use those regimens in patients who have borderline operable disease in cases where [we] want to see a higher response up front to enable use of more aggressive local therapies if they have a good response.

Most of us, now that we have ramucirumab enhancing the effectiveness of second-line paclitaxel, usually reserve taxanes for second-line treatment. That treatment strategy is based on data from Europe. Most of the patients in the United States with gastric cancer are in their 60s and 70s; they are older patients. There was one randomized trial conducted in Germany where investigators looked at 5-fluorouracil and oxaliplatin with or without docetaxel specifically in patients over the age of 65. They saw no survival benefit for older patients getting 3-drug versus 2-drug therapy, and they had a lot more toxicity.

Generally, I would use an age cutoff. For patients over the age of 60, I would try to avoid triplet regimens. I would reserve selective use of triplet therapy for younger patients with good performance status. Also in metastatic disease, epirubicin was really disavowed in NCCN guidelines on metastatic disease. There are a number of studies that show that 2-drug chemotherapy regimens are just as good as 3-drug regimens with the addition of epirubicin. Epirubicin adds lots of side effects, so NCCN guidelines really discourage the use of epirubicin in the treatment of metastatic disease because it is not clear that epirubicin adds any benefit over 2-drug chemotherapy.

I should also make a point with the early-stage disease that there are some studies suggesting a possible uptick of [the] incidence [of] gastric cancer in younger patients. There does seem to be some unexplained trend that we may be seeing gastric cancer incidence increase slightly in

younger patients. Some hypothesize that this is a demographic issue because we are a very heterogeneous country. A lot of people come to the United States from around the world. Whether the increased incidence of gastric cancer in younger patients is a reflection of changing demographics is unknown. We do know there may be a slight trend toward an uptick of gastric cancer in younger patients, but it is not a clearly established trend yet.

Of course, the other issue is being aware of familial risk. We do see, sometimes, an association of gastric cancer with Lynch syndrome or familial colorectal syndrome. There is an [established] entity called *CDH1* mutation gastric cancer, which is very rare, but you see generation after generation in these families with [an] early age of onset [of] gastric cancer, which is attributed to the *CDH1* mutation. It needs to be identified in high-risk families because these are patients that you would actually send for prophylactic gastrectomy in their 20s or 30s to try and prevent a very high risk of developing gastric cancer if they carry this genetic mutation.

AJMC®: Discussing fundamental principles trying to manage gastric cancer across lines of therapy, from early-line therapy to late-stage therapy, what is the best way to start therapy and manage treatment across lines of therapies to maximize survival?

DR ILSON: You have to start with *HER2* testing. If patients are *HER2*-positive, trastuzumab should be included as part of the first-line chemotherapy. Most patients should get first-line fluoropyrimidine treatment and platinum-based chemotherapy. That could be typically involve using folinic acid, 5-fluorouracil, and oxaliplatin (FOLFOX) or capecitabine with oxaliplatin. This is less utilization of infused 5-fluorouracil and cisplatin. That regimen has really been replaced by FOLFOX or capecitabine with oxaliplatin first-line, with or without trastuzumab. Second-line therapy, regardless of *HER2* status, would involve giving patients paclitaxel plus ramucirumab. Then, third-line therapy involves using irinotecan-based treatment, and if we get regulatory approval of nivolumab, that is going to be a new third- or fourth-line treatment option.

I think we are starting to see similar progress that we saw in colorectal cancer—that we are extending survival out around a year—and I think that if oncologists apply the lines of therapy, we are going to get patients out further and extend survival out longer. But the benefits are quite modest. In terms of genomic profiling, that still remains a research approach. I cannot say about genomic profiling to date that the data indicate a high yield to identify targetable mutations or clearly guide patients into clinical trials, »

but we are accumulating a database of genomic profiling of esophagogastric cancers. We are learning that [there] are molecular subsets of these diseases, and there are leads in terms of mutations that might be targetable, but at the current time, it still remains a research approach. I cannot say that we profile patients and we can get an answer about what molecularly targeted agents we should give patients, with the exception of *HER2*, but you don't need genomic profiling to identify *HER2*-positive patients. To identify *HER2* mutations, you can just do immunohistochemistry and fluorescence in-situ hybridization testing.

AJMC®: In Japan, as you mentioned earlier, D2 lymphadenectomy is a more common surgical approach, whereas in the United States, D1 lymphadenectomy is more common. What are some of the fundamentals of surgical treatment as they are applied in the United States versus abroad?

DR ILSON: Academic centers in the US advocate for removal of at least 15 lymph nodes. Patients really should be referred to referral centers that have high-volume surgical flow because community

surgeons who do gastrectomies a couple of times a year are not really versed in doing D1 or D2 gastrectomy. And there are a lot of outcome data, certainly for these rare cancers, that patients tend to have better outcomes when they are treated in high-volume centers. There is also an increasing rate of using laparoscopic and robotically-assisted [gastrectomies], which is increasingly moving into more locally advanced disease. Initially

that approach was validated in early-stage gastric cancer in Asian studies, but now we are seeing, increasingly, the adoption of laparoscopic and robotically-assisted gastrectomies, even in more locally advanced disease.

AJMC®: Where do you see the future of gastric cancer in the next 5 to 10 years in terms of surgical treatment, detection, and pharmacologic treatment options?

DR ILSON: In the next 10 years, I think there will be more of a universal adoption of staging laparoscopy to identify metastatic disease in patients early on that probably will not benefit from surgery. I think there will be an increasing adoption of more laparoscopic and robotically assisted [gastrectomies], which I suspect is going to lead to less postoperative morbidity and complications. I think there will hopefully be the identification of new targets to incorporate into adjuvant therapies. I think we have reached the ceiling in terms of benefits of adjuvant chemotherapy treatment, which results in an approximately 10% to 15% survival improvement, which is not a lot. I think we need to identify new systemic agents that we can add to adjuvant therapies, and the targets right now look like *HER2*-targeted agents, checkpoint inhibitors, and *VEGF*-targeting drugs. Those certainly, hopefully, will be studied, and we will have to see whether or not they add benefit.

Then there is the issue of monitoring patients' disease. It has typically been with imaging and endoscopy, but we are getting into the era now of liquid biopsies and following circulating tumor DNA. That has the advantage of monitoring patients' disease mutational status real-time. For example, in *HER2*-positive patients, when they become refractured to trastuzumab, data from our institution indicate about 25% of patients on repeat biopsy become *HER2*-negative. Use of technology, like circulating tumor DNA, will allow us to monitor in more real-time what the mutational status of the patient is, if they are evolving mutations, and if they are losing expression of targets.

Whether or not we can use these technologies to monitor for minimal residual disease or recurrence is probably going to bear more fruit in colon cancer because we have more active therapies. You could argue, "Does it really matter if we identify metastatic disease recurrence subclinically if we don't have treatments for it?" But I think that technology is going to be increasingly developed. Positron emission tomography scan imaging may be helpful in imaging and response assessment. Studies are ongoing, but I think new systemic therapies are the key. In terms of making sure patients get optimal surgery, with D1 or D2 lymphadenectomy, and with whether or not they benefit from minimally invasive surgeries, I think there is going to be an advance. ■

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