Podcast transcript
Non-metastatic gastric and GEJ cancers: clinical case discussions ep.1

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Transcript

Sam Klempner
Hello, and welcome to this. GI CONNECT podcast on gastric cancer. My name is Sam Klempner, I'm a GI Medical Oncologist at Massachusetts General Hospital in Boston and I'm joined by my colleague and international gastric cancer leader, Dr Lizzy Smyth.

Elizabeth Smyth
Thanks, Sam. Thanks for the introduction. Hi, everybody, thanks for joining us today. I'm Lizzy Smyth. I am a GI Medical Oncologist in Oxford, United Kingdom, and thanks for the invitation to speak here.

Sam Klempner
So we're gonna go through a couple of cases that I think will highlight some current data and emerging themes both in the non metastatic and metastatic settings. So, Lizzy, if you want to lead us off with your case.

Elizabeth Smyth
Sure. So the first case that we're going to discuss is an operable localised gastric cancer. So the case is, a 68-year-old patient presents with this dysphagia, difficulty swallowing, and a 3kg weight loss. So, this is a fairly typical patient

Endoscopy shows a circumferential tumour at the gastroesophageal junction. The biopsy shows a poorly differentiated adenocarcinoma.

Patient has a past medical history of reflux, also very common, and he is an ex-smoker, but quite fit. Family history of a mother having breast cancer in her seventies. Exam totally within normal limits. Routine staging of a CT TAP shows a T3 N1 tumour and PET shows no metastasis. So here we are with a locally advanced junctional adenocarcinoma.

Sam, I would like to ask you, what's your practice? What biomarker should we absolutely test in locally advanced GE junction cancer or gastric cancer?

Sam Klempner
Yeah, it's a great question and very topical, and probably I may have a different answer in a couple of years, when maybe we'll have more biomarker directed therapies in the non-metastatic setting. But I think that over the years that we've learned, and you've led some of this work, certainly the microsatellite high, or the MMR deficient patients is a somewhat different subgroup. Not only do they have an intrinsically better prognosis, but of course, from the metastatic setting we've learned that they are in general, substantially more sensitive and more likely to benefit from immune checkpoint inhibitors.

So our institutional practice, and I think something that should strongly be considered internationally is the need to test all localised or locally advanced gastric and GE junction cancers for mismatch repair status. At our institution, we do test for HER2 and PD-L1 in the non-metastatic setting, but admittedly, are not routinely acting on those biomarkers.

Elizabeth Smyth
I do think that's the key. So although, as you say, in a couple of years, it's likely that we'll be testing for HER2 and PD-L1, at this moment in time we're not acting on those for our patients who are going to have surgery. MSI or MMR is slightly different because it impacts on the prognosis of the patient, on the likelihood of that patient to benefit from chemotherapy. So, I do think that that's useful information to have and we do recommend it for stomach and junctional tumours. We know that, you know, the distal stomach cancers are more likely to be MMR deficient, but we also see a small proportion, maybe 3 to 4% of junctional adenocarcinoma being MMR deficient. So, I think it's important to recommend the test, and that's independent of whether the patient has a family history, because we know that most MMR-deficient patients with gastric cancer are sporadic rather than genetic.

So we do an MMR test for this patient, and it's MMR proficient as most patients are. So I would like to ask you, Sam, what would your preferred treatment approach be for a fit 68-year-old gentleman with an operable GE Junction, which is node-positive? So we've got a T3 N1 tumour, what would your approach be?

Sam Klempner
Yeah. So this is a very typical something that we would see in the clinic. You know, you have a clinically node-positive patient, stage 3 clinically. And really, what do these patients die of? What is the main problem? Well, node positivity is obviously a marker for risk of distant metastases, which is the main cause of death. Most of our patients die of recurrent disease. So really strategies that are geared towards addressing occult micrometastatic disease and reducing the risk of recurrence which, in my opinion, is really dependent on the activity of our systemic therapies. And perhaps one of our most active systemic therapies is FLOT. So, our general approach to a fit, stage 3 patient with node-positive GE junction cancer would be active systemic therapy with FLOT, as was studied in the FLOT4 trial.

Sometimes we'll have investigator or industry sponsored trials to address this population. There's certainly a need to improve upon FLOT, and even at ASCO just a couple of days ago, we saw an early press release about the MATTERHORN Trial, which is exactly trying to build on FLOT by adding an immune checkpoint inhibitor in the neo-adjuvant and adjuvant components of FLOT. But to answer your question, our standard approach in this situation involves active systemic therapy and evidence-based care with FLOT based approach.

Elizabeth Smyth
Thanks, Sam, and I think we would be very much in line with that. But I think we should also mention that there is another standard of care which is frequently used, and that's chemoradiotherapy. So we have 2 choices in this setting: FLOT, a perioperative chemotherapy, and as I tell my patients we cure about half of patients who we treat with FLOT and surgery; and then there's chemoradiotherapy, as you mentioned, based on the CROSS trial, which also cures about half of patients. But we do have this sense that in CROSS there was squamous cancers and adenocarcinoma, and the benefit is much greater for squamous cancers with chemoradiotherapy than for adenocarcinoma.

And I think what's been really key for me over the past year is to see the 10-year follow-up of CROSS. Which showed, in fact, that distant metastases which you were relating to, were not reduced by the chemotherapy in CROSS. So, we know that with CROSS we've got relatively little chemotherapy for about 5 weeks, given on a weekly basis. It's really acting as a radio sensitiser, and it's allowing that high path CR rate that we see with chemoradiotherapy. But what we don't see is that reduction of micrometastatic disease and distant recurrence. So I completely agree with you, for node-positive patients, I think that perioperative chemotherapy is a better choice. I would say that they haven't been compared yet in clinical trials. So we do have the ESOPEC trial coming up, maybe in the next year or so, to tell us which of those options is better, or whether they are equivalent

You mentioned the MATTERHORN trial, and that's just been presented at ASCO. So where do you think we're going with, first of all, immune checkpoint inhibitors and then maybe targeted therapy in the perioperative setting?

Sam Klempner
Yeah, I think this is really the way forward for our tumour-type of interest. We know that with appropriately selected targets in patients in advanced setting, we can improve the survival by incorporating checkpoint inhibitors, or targeted therapies, or even combination therapies, like in KEYNOTE-811, where perhaps you're leveraging both potential advantages of targeted and immune therapies, and maybe even some cooperativity between the two.

I would only make one additional point about the management of the earlier case is that I think a lot of us recognise how difficult it is to give FLOT in the adjuvant setting, and we will sometimes tweak and give like 6 upfront and 2 out back, as opposed to the 4 and 4 that was studied. Admittedly, there is not as much data for that but I think in practical management sometimes we will do that.

But to answer your question, I think it really comes back to the idea of doing all we can to address systemic disease and neo-adjuvant immunotherapy has some biologic rationale when the tumour is in situ, there is a more diverse T cell response, as we've seen from some other tumour types and certainly the clinical activity with neo-adjuvant checkpoint inhibitor is quite promising.

So I expect that most of the strategies will push on the neo-adjuvant component in maximising the effectiveness of our therapies there. I suspect all of the biomarkers that have been explored, and are being explored in the metastatic setting, including the emerging ones of claudin 18.2 and FGFR2, which I know you've been involved in for a while, will hopefully move into the non-metastatic setting with the idea that we can take the activity in advanced disease, and translate that to earlier stage disease. Of course, we have to prove that and do these important trials, and I really do think that that's going to be a big part of the pathway forward.

Elizabeth Smyth
I agree, I think, that we're going to have quite an interesting time, and hopefully help more patients, as we introduce these treatments into the perioperative setting. As we said, we're there in metastatic disease, but right now, just to be clear for HER2 and PD-L1, we're not using those targets in the perioperative setting because we don't yet have the data. We're waiting for the readouts from the trials. We've seen data on pathological complete response, but not yet data on event-free survival or overall survival. So, we're waiting for those, hopefully at some upcoming meeting, before practice can change.
So, we've talked about that standard case. Let me prod you a bit on what you would do for selected populations. You've mentioned already, of course, that you're kind of leaning towards a total neo-adjuvant approach, and I appreciate that because we know that only 50% of patients tolerate their treatment after surgery. I think there is a few concerns about the total neo-adjuvant approach, putting 8 cycles of FLOT upfront in terms of neuropathy, perhaps, or deconditioning before surgery. But certainly, that's something that's being looked at and it's been very successful, for example, in rectal cancer, as we know, and they are also clinical trials looking at that neo-adjuvant setting like CRITICS-II and other studies in development.

So what about older patients? So we know clinical trials patients, average age 62. Non-clinical trials patients, average age 70s, maybe even a little older. What would you do if you've got, you know, an 82-year-old, with the general comorbidities of an 82-year-old? He presents with the same disease. Do you change your treatment? Are we concerned about FLOT in older patients? Do we use more chemoradiotherapy? What's your approach?

Sam Klempner
Like all of oncology care this is, of course, a shared decision-making with the patients and our job is to introduce the options and provide a balanced assessment and realistic expectations of what each strategy might achieve.

I think the principles are still broadly similar in terms of trying to reduce the risk of recurrence by acting on the systemic disease. But the way to get there may differ a little bit.

As you suggested we have seen that FLOT can be given safely to fit older patients. Age itself is not a clear criteria but co-morbidities and toxicities do increase with age, and we do know that FLOT is more difficult to tolerate, perhaps, in some of this patient population.

I would say, in the real world practice we will sometimes lean towards a little less of the upfront chemotherapy. I've considered platinum doublet as opposed to the triplet with FLOT in some cases. And perhaps a more CALGB 80803 like approach is something we will often consider where it's, for example, FOLFOX followed by imaging, followed by consideration for chemoradiation.

And I think the potential advantages of this strategy. One - we know that there's clinical activity from the trial, and two - in case the patient does not go to surgery or chooses not to go to surgery in this case because of toxicity or patient preference you have, in that scenario, given definitive therapy in the form of chemoradiation. So you're a little bit buffered against what to do in case the patient chooses not to go to surgery.

Perhaps, I would say globally, a little bit more of the CROSS-based approach in the elderly patients. And that's certainly a very evidence-based, and phase 3 data-supported approach. So absolutely nothing wrong with that. I don't know, what is your practice in the older patient population with comorbidities?

Elizabeth Smyth
I think that actually when we're in our upper GI MDT, the biggest stressor for any patient is the surgery. So, the bottom line is, if a patient is suitable for an esophagectomy, I feel that they'll probably tolerate chemotherapy. Now, that doesn't mean that I'm going to give 100% FLOT. So, for patients over the age of 75, I will try FLOT, but I'll routinely reduce the dose by at least 20%. And, as you say, really need a clear focus on toxicity as we go along and keep a very close eye on them.

I think, as you say, for me, if they're are node-positive maybe chemoradiotherapy is going to be less effective. But maybe when we get into the super elderly thinking about chemoradiotherapy, with that view to definitive treatment if we're concerned that they won't get through surgery. That's a very appropriate approach. I think we need to be flexible and approach this based on the individual and, you know, we can have a fit 85-year-old and a less fit 50-year-old, and we approach all our patients as individuals and try and give them the best treatment that they can, and make those decisions with them.

Another cohort of patients. We touched on MMR deficient patients a little while ago, and we're routinely testing for that. We've seen amazing results for the neo-adjuvant treatment of MMR deficient patients with nivolumab and ipilimumab, and also with durvalumab and tremelimumab in two trials, NEONIPIGA and INFINITY. What do you do with your MMR deficient patients? Are you tempted to use neo-adjuvant immune checkpoint inhibitors?

Sam Klempner
Yeah, I find this data very compelling. Both the sort of pooled meta-analysis suggesting a lack of benefit from perioperative, in this case MAGIC or adjuvant strategies such as CLASSIC.

Certainly, FLOT was not included in that meta-analysis, but I think the totality of the data is suggestive strongly that these patients derive less benefit from chemotherapy-based strategies. They clearly have a more favourable prognosis overall. And the data with the neo-adjuvant trials that you mentioned is like really impressive. I mean, to see 3 months of neo-adjuvant immunotherapy in the NEONIPIGA trial yield pathologic, complete response rates of, you know, 60% and major path response rates into the mid-70s. I know it was early reporting, but if you look at the event-free survival curve it's basically a flat line. I mean, we would love to see something like that for more of our patients.

So not only am I tempted, but we actually routinely do give neo-adjuvant immunotherapy to this patient population. We also discuss upfront surgery and consideration of adjuvant immunotherapy, or just observation and surveillance because the surgery is of course, a major event, but immunotherapy is not completely without side effects. So subjecting someone to a year of adjuvant immunotherapy, when they may do quite well with surgery alone is a discussion. But yes, I feel that IO needs to be part of mismatch repair deficient localised disease. We tend to give it in the neo-adjuvant setting whenever possible.

Elizabeth Smyth
I am so happy for your patients, and so jealous that you are funded to give neo-adjuvant immune checkpoint inhibitors. That's fantastic. We're not funded here in the UK for that, and I think we'll need to wait for larger trials, unfortunately.

But you're right to say that the patients with MMR deficient cancers might just need surgery, and their prognosis is really pretty good with surgery alone. Certainly, platinum and 5FU chemotherapy does not appear to be effective. I would say that for the patients who we need to downstage, and we don't have access to immune checkpoint inhibitors, the data from a small cohort of FLOT treated patients who are mismatch repair deficient was not bad. So don't forget we've got a taxane in FLOT that is working on a different pathway in the cancer cell, and the mismatch repair deficient tumours appeared to be a little less resistant to that. Good pathological complete response rates with FLOT. So, my gut feeling when we don't have access to neo-adjuvant immunotherapy is, if the patient does not need to be down staged, for example, if it's a distal gastric cancer and the patient is a little older, straight to surgery, if we can. If the patient does need to be down staged, for example a junctional cancer, FLOT is probably the best way forward. And if we can enrol our patients in trials with checkpoint inhibitors, all the better to try and get to those excellent pathological complete response rates.

And I guess the next step will be, do we need to do surgery? Because, you know, to a degree they're already there in colon cancer thinking about a non-operative approach? I think that's very experimental for now but do you see that being the way of the future?

Sam Klempner
Yeah, I do and I think, you know, this could get even a little bit more confusing when we have data for, like, KEYNOTE-585 and MATTERHORN and have the MSI patients in there. Because they're probably going to do great, and then you're going to wonder if it's chemo plus IO or IO alone.

But yes, I think stratifying and teasing apart the patients who do exceptionally well after neo-adjuvant therapy and may be able to move forward with the non-operative approach is a key question to the field. Certainly, I believe there's an arm of the INFINITY trial that is addressing this question, which was really great to see, and that that's a wonderful trial being run by our Italian colleagues.

The tools we have right now are probably not routinely good enough to tease apart those patients yet. Meaning PET scans, endoscopic assessment, with maybe bite-on-bite biopsies to look for complete clinical responders. And ultimately this is a place and an opportunity for plasma-based approaches like cell-free DNA, and I know you've had some nice papers about looking at the prognostic performance of ctDNA, and it's been an interest of ours as well. So I think, yes, that's definitely the direction we just need to get better at teasing apart these patients so we don't forego a curative procedure in someone who needs it.

Elizabeth Smyth
And would do very well afterwards. So I do think it's a fascinating question. Of course, the patient needs to be involved in these decisions, because a gastrectomy is a life-changing operation. So if we can avoid it, if we can avoid it in future, I think that that's something that's definitely going to be of interest.

You have just mentioned ctDNA, so, hot topic, you and I have both done research on it. And so I'm going to put to you a little part of this case and ask what you would do next. So our patient, our hypothetical patient we've been discussing, they've had FLOT, they've had their surgery, and they've tolerated it pretty well. Their post-operative histology yp T2 N2. So they've got 3 lymph nodes involved, and they've had a decent lymph node resection, 42 lymph nodes out. So what do you? What would you do next for this patient? Are you routinely using ctDNA? If not, why not? Should we use it? Where do you think we're going to go with that?

Sam Klempner
This case highlights a lot of things. Certainly high-risk residual node positive disease after surgery, we know these patients are at high risk of recurrence. ctDNA can even further refine that risk. So it's pretty clear to me from your work, and our work, and others that patients who are ctDNA positive in the period after surgery, whether you define that as one test draw, a couple of draws within the first 2 months, or whatever, those patients are at exceptionally high risk of recurrence, probably upwards of 80% or more. And that just tells you that, one - we have a relatively sensitive test, and two - that this is a conserved poorer prognostic biology, these patients presumably have micrometastatic disease somewhere.

The question of what to do about it is the million-dollar question. So, we know that we need to worry, and these patients are at very high risk, but we don't yet have data to tell us what is the best thing to do. Certainly, we would try to offer this patient the adjuvant component of FLOT, that would be the routine standard of care. It's tempting to consider other strategies but admittedly we don't have large data sets to say, non-cross-resistant chemotherapies, or adding IO really improves outcomes. We are doing ctDNA in these

scenarios, partly to build the global data sets that will help us guide the future in terms of designing some of these trials for, you know, particularly high-risk subsets like ctDNA positive. But admittedly, we are not routinely guiding management based on ctDNA in this setting yet.

Elizabeth Smyth
I agree. So, I think that we're a little bit, maybe, behind colorectal cancer in this sphere In terms of the trials which have been done, we have reasonably sized data sets, but very little collected prospectively. I'm really delighted to hear that you're testing in Mass General ctDNA. I'm interested, without getting super technical, which assays do you think we should be using? Should we be using personalised assays? Or should we be using non-personalised assays? I haven't seen a huge amount of difference between them yet which really surprised me.

Sam Klempner
The technological and analytical aspects of these platforms continue to improve and will probably incorporate even other features, methylation, proteomics, etc. And I think that that will, both platforms will achieve, you know, high sensitivity and specificity.

The issue with, in my experience with, disease types where patients get a lot of neo-adjuvant therapy is that, to build a patient-specific assay at some point you need tissue for, generally whole exome to benchmark and define the variants you're going to track. And if the only tissue you have is a small endoscopic sample at diagnosis, and then hopefully the patient has a good pathologic response at surgery. There are cases where you just won't have enough material to build the test and this may be an opportunity for plasma-based assays, although I do expect that the tissue-based platforms will continue to get better with, you know, smaller input values and things like that. But I think those are, sort of, some of the questions that may guide you towards one platform or another.

Elizabeth Smyth
I agree, I think, that we're still evaluating, aren't we? I would say the question is easy, almost, for the ctDNA positive patients, those patients who are at high risk of recurrence. So, we are definitely going to treat them if we can. The question is, should we be evolving other treatments than FLOT? And how good is FLOT for those patients who still have residual disease based on ctDNA after surgery? I don't think we know the answer to that yet. But what I do think is possibly it gives us an opportunity to bring some of these very effective and powerful new drugs that we're using in the advanced disease setting maybe a little bit earlier into treatment. So, for example, I've got a study coming up with trastuzumab deruxtecan in ctDNA-positive patients, and I'd be really interested to understand whether we can use ctDNA, a fall in ctDNA, as a measure for how effective the drug is and it could give us an opportunity. You know, traditionally, drug development has been done in patients who are very refractory to treatments, and they may have a different biology than patients who've just had surgery. And I think it does give us an opportunity, perhaps, to help patients at an earlier stage in their treatment pathway. But those are all interesting questions. I don't think we're there yet, but certainly something to keep an eye on over the next couple of years.

So I do hope it will offer us an opportunity to help patients actually, with minimal residual disease. And I think that we will hopefully be classifying these as a separate group and future, in whom we can possibly cure a micrometastatic disease with the right treatments. But I think we'll need to return to that subject after a while.

So that's been a great case. That's been a really detailed discussion of a perioperative case moving through their treatment journey with FLOT with post-operative treatment. Thinking about biomarkers. Is there anything else you wanted to add to that, Sam? Any final thoughts in the operative setting?

Sam Klempner
No, I think it's getting into defining the patients who are benefiting, teasing apart the groups that we can approach differently and really testing for MMR deficiency, I think, is the key thing that you can implement in practice like right away as a way to identify a group that maybe we already can manage differently.

Elizabeth Smyth
Thanks, Sam.