ASCO: Advances in the Management of Gastrointestinal Cancers

By Andrew M. Lowy, MD [5]

As part of our coverage of the ASCO Annual Meeting, we discuss advances in the management of upper gastrointestinal (GI) tract tumors, as well as highlighting clinical trial results that will be reported at the meeting.

As part of our coverage of the 2014 American Society of Clinical Oncology (ASCO) Annual Meeting, held May 30–June 3 in Chicago, we are speaking with Andrew Lowy, MD, director of surgical oncology at the University of California, San Diego Moores Cancer Center. Dr. Lowy manages patients and does research mainly on cancers of the pancreas, liver, and the gastrointestinal (GI) tract. He will be providing an overview of the biology and advances in biomarkers for upper GI tract tumors at the meeting on June 2. Today we are discussing advances in management of upper GI tract tumors, as well as highlighting clinical trial results that will be reported at the meeting.

—Interviewed by Anna Azvolinsky

Cancer Network: Let’s start with the main types of non-colorectal GI tract cancers. There are quite a lot of these. How are they distinguished, and at what stage are these malignancies typically diagnosed?

Dr. Lowy: As you said, there are a number of malignancies when you are talking about non-colorectal GI tract tumors. The simplest way to divide them is by the foregut, which is the esophagus, stomach, and the upper part of the small intestine, and then the pancreatic and biliary system, which is the pancreas, bile ducts, gallbladder, and generally the liver. Those are the major ones and there are other, more uncommon types of malignancies, but for the most part, these are the ones we are talking about. As far as stage of diagnosis, worldwide, one of the most difficult problems treating these malignancies is that they tend to be diagnosed at later stages. Aside from stomach and esophageal cancers in Asia, where there are some screening programs because of the high incidence and diagnoses that tend to occur a bit earlier than in Western countries, for the most part, these are malignancies that are diagnosed very late and are difficult to treat.

Cancer Network: Can you highlight any new surgical techniques for these types of tumors that have been developed over the last few years?

Dr. Lowy: Sure. Broadly, the direction in surgery has been towards a more minimally invasive approach to treating all types of cancers within the abdomen, and certainly the non-colorectal GI cancers are no exception. Surgery for these types of cancers is a bit more complex than for colon cancer, so the surgical techniques have taken more time to evolve but they are rapidly gaining acceptance. For instance, laparoscopic surgery for both esophageal and stomach cancers has become more commonplace. Certainly, in Asia, it is very widely applied at this point and it is gaining traction in the United States as well. The same can be said for pancreatic surgery, where surgeries for cancers on the left side of the pancreas have become very common. Our group published a paper this year looking at the trends associated with the use of laparoscopic surgery, and it clearly shows a marked increase year by year in the last 5 years. And now, laparoscopic surgery is applied to liver surgery, and even complex hepatic resections are being done using minimally invasive techniques. The advantage and the rationale is that the incisions are part of the significant morbidity associated with the operation. Also, surprisingly, it appears that using minimally invasive techniques affords better exposure of the anatomical structures, which are necessary to visualize well during the operations.

Cancer Network: Stomach cancer is one of the most widely diagnosed cancer types around the world but it has not been studied as extensively as other cancer types, at least not in the United States. What do we know about the biology of stomach cancer? Are there any biomarker-defined subtypes or other information that has emerged recently?

Dr. Lowy: Stomach cancer is the second leading cause of cancer death around the world, which many people in the West don’t realize because it is not such a common disease here. But it is a...
major worldwide health problem. It has been a difficult disease from the standpoint of understanding its molecular biology. Unlike some other diseases, like pancreatic cancer, where there are a couple of specific mutations that occur in almost every tumor, in stomach cancer, at least at this point, what we know to be the most common mutation, which is in the p53 tumor suppressor gene, is present in less than half of the cancers. There is not any one single cardinal mutational event.

That being said, the evolution of biomarker-driven treatment has actually proceeded faster than for some other cancers, and this is because of the recognition that a subset of the cancers, probably in the 15% to 20% range, overexpress the ERBB2 or HER2/neu protein. That is the protein that most people are familiar with in the treatment of breast cancer, where it is overexpressed in about one-third of breast cancers. It is a cell surface receptor in the EGF receptor family, and it can be targeted via monoclonal antibody therapy. The most commonly used and widely known is trastuzumab, which was shown in a study presented at ASCO previously; it improves the survival of patients with metastatic stomach cancer, and in particular, patients whose tumors overexpress the protein. HER2 is an accepted biomarker to guide the systemic therapy of advanced stomach cancer.

The studies that we are waiting for, which are not yet mature, are those that are trying to understand whether trastuzumab is an effective treatment in earlier-stage stomach cancer. Those studies have not yet been completed. But at this year's ASCO meeting, there is an exciting presentation that documents the efficacy of a monoclonal antibody to the vascular endothelial growth factor receptor-2 (VEGFR-2), a drug called ramucirumab, which has also been shown to prolong survival in patients who have been previously treated for metastatic gastric cancer with chemotherapy. So, it appears that there is another biologically targeted drug that has efficacy. Again, it will remain to be seen whether there are specific molecular biomarkers that can predict which subset of those patients treated with the drug benefit the most and whether that drug and others like it will have a role in earlier-stage disease.

**Cancer Network:** What about esophageal cancer? What are the advances in understanding this type of tumor?

**Dr. Lowy:** At this year’s ASCO meeting, there is a trial that utilized the same VEGFR-2 antibody, which, unfortunately, in esophageal cancer did not show the same magnitude of benefit. At this point, we don’t have molecularly targeted agents in esophageal cancer that have the same activity as in gastric cancer. The standard of care, which has evolved in esophageal cancer over the last several years, has been that for patients who are operable, preoperative chemotherapy and radiation therapy should be administered—that is for esophageal adenocarcinoma, which is the most common type in Western countries. We are a bit farther behind in understanding molecular biomarkers, but we are reaching the stage where preoperative therapy has become the standard, and the other change is to move towards minimally invasive procedures for esophageal cancer surgery.

**Cancer Network:** Are there any other clinical trials for non-colorectal cancer tumor types that will be reported at this year’s ASCO meeting that you want to highlight?

**Dr. Lowy:** I think there is one very interesting study in pancreatic cancer, which utilizes a new drug that targets the JAK1 and JAK2 proteins. This is a study that was done in patients who had failed multiple lines of prior chemotherapy and that have rarely been studied because, as most people know, patients with pancreatic cancer, unfortunately, only have a relatively short survival, so, in the past, patients who didn’t respond to initial chemotherapy rarely got a second and third line of therapy. What is interesting about this trial is that it looked at the use of this drug added to chemotherapy and it showed a marked improvement in survival for patients who expressed a very simple biomarker, the C-reactive protein (CRP), which is a general measure of systemic inflammation. The JAK1 and JAK2 pathways are inflammation regulators, and the thinking is that these drugs are essentially reducing the level of inflammation, which is associated with cancer cachexia—the propensity of patients with pancreatic cancer and other cancers to lose weight rapidly and not be able to sustain their nutrition. This study showed that, for all of the patients, there wasn’t a major improvement in survival, but when you looked at the subgroup that had this cachexia-like syndrome and elevated CRP, there was a marked improvement in their outcomes. But what is also interesting is that this study suggests that these drugs are not necessarily targeting growth of the cancer so much as they are targeting the effect of the cancer on the body, and so people live longer with that drug. And if that is true, this represents a bit of a shift in the way we think about cancer treatment, in terms of treating the effects of the cancer rather than necessarily targeting the cancer itself.

**Cancer Network:** Thank you so much for joining us today, Dr. Lowy.

**Dr. Lowy:** You are welcome.
References:


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