Ovarian Cancer 10-Gene Biomarker

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Ovarian cancer is the fifth leading cause of cancer death among women in the United States and has the highest mortality rate of all gynecologic malignancies. Each year, approximately 21,880 women are diagnosed and 13,850 women die from ovarian cancer.

The standard of care for ovarian cancer is aggressive cytoreductive surgery followed by chemotherapy with platinum and taxane. Despite initial favorable responses, 65 percent of these patients recur with chemoresistant cancer during the first three years and succumb to disease. Currently, there is no diagnostic tool that identifies patients who have a high likelihood of recurrence, and treatment options are very limited for these patients. To improve patient survival, it is necessary to develop a reliable test to identify patients with poor prognosis and provide them with targeted therapy at an earlier point in the disease.

Recent research at Cedars-Sinai demonstrated that high expression of 10 genes (AEBP1, COL11A1, COL5A1, COL6A2, LOX, POSTN, SNAI2, THBS2, TIMP3, VCAN) correlates with poor overall survival in ovarian cancer. This study included a total of 710 high-grade, advanced-stage serous ovarian cancer samples, the largest sample size used to date for discovery and validation of a gene biomarker panel. The 10 biomarker genes discovered in this study are strongly associated with poor overall survival. We postulated that some of the genes we discovered are not only biomarkers of poor survival but also active contributors to poor survival. The majority of the 10 biomarker genes are not expressed in normal ovaries, but their expression is enriched in metastases and even further enriched in recurrent metastases. These genes are also biomarkers of metastatic progression and poor survival in other

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Cholangiocarcinoma refers to the class of adenocarcinomas arising from biliary epithelium, and as such, cholangiocarcinoma can occur anywhere from the distal common bile duct in the ampulla of Vater to the peripheral intrahepatic bile ducts. Current systems for categorizing cholangiocarcinomas are based on location, morphology and treatment options. A simple working system is to consider those occurring below or distal to the biliary bifurcation as extrahepatic or distal cholangiocarcinomas, those occurring at or near the biliary bifurcation as central cholangiocarcinomas and those occurring in the liver as intrahepatic or peripheral cholangiocarcinomas. While the mainstay of treatment for almost all forms of cholangiocarcinoma remains complete surgical resection, many tumors are not amenable to resection due to involvement of major hepatic vascular or biliary structures or due to excessive hepatic parenchymal involvement.

**Distal cholangiocarcinoma**

Many of these tumors will manifest in a manner similar to other periamputal tumors with signs or symptoms of obstructive jaundice. Those amenable to resection should undergo pancreaticoduodenectomy (for distal bile duct lesions) or resection of the extrahepatic bile duct with hepaticojejunostomy (for mid-bile duct lesions). In cases of portal vein involvement or common hepatic artery involvement, resection can often still be undertaken with concomitant vascular reconstruction. The development of new neoadjuvant protocols coupled with improvements in surgical techniques have led to greater rates of successful resection, but local and distant recurrence rates remain high.

**Central cholangiocarcinoma**

These tumors are often referred to as Klatskin tumors after Gerald Klatskin, MD, who first grouped these uniquely challenging tumors together 50 years ago. These tumors have various manifestations (Fig. 1) and by definition involve hilar structures. Complete surgical resection is often not possible because of tumor involvement of bilateral portal vein or hepatic arterial branches or biliary involvement that extends into segmental branches. In most cases, surgical resection should be the first consideration, and this will often require hepatic lobectomy to obtain clear margins. Vascular reconstruction and complex biliary reconstructions, sometimes involving separate anastomoses to as many as six segmental bile ducts, may be required. If surgical resection is technically possible but would not leave behind a sufficient amount of functional hepatic remnant, preoperative embolization of the portal vein of the involved lobe of liver can be performed, resulting in atrophy of the embolized lobe and compensatory hypertrophy of the uninvolved lobe. Increase in...
planned liver remnant volumes of 50 to 100 percent can occur in as little as six weeks, which may in turn allow future surgical resection (Fig. 2).

In central cholangiocarcinomas not amenable to resection, several options should be considered. Liver transplantation has increasingly gained acceptance as an alternative in highly select cases. Data from a number of centers has demonstrated that in carefully selected patients, transplantation is accompanied by approximately 80 percent five-year cancer specific survival, which generally surpasses the results reported for resection.12 This data has led to changes in organ allocation policies, which give added transplant priority to patients with Klatskin tumors that have undergone aggressive neoadjuvant treatment. Important caveats include the exclusion of any patient with lymph node metastases and the exclusion of any patient who has undergone prior attempt at resection or who has had a biopsy of the tumor by a transperitoneal approach (either image-guided or by endoscopic ultrasound). Liver transplantation is especially valuable in patients with cholangiocarcinoma arising in the background of primary sclerosing cholangitis, as the recurrence rates with resection alone are exceedingly high in these patients due to diffuse at-risk biliary epithelium. Novel alternatives to resection or transplantation in unresectable central tumors include several local therapies, including intraductal brachytherapy, external beam radiotherapy and intraoperative tumor ablation with a nonthermal modality known as irreversible electroporation (IRE). Survival outcomes of multimodal treatment regimens can, in some cases, approach or even surpass that of resection due to the slow-growing nature of these tumors combined with the lower risk profile afforded by some non-resection strategies.

Peripheral cholangiocarcinoma
The large number of local and regional therapies available for treating various other hepatic malignancies can also be applied to treating peripheral cholangiocarcinomas. Once again, surgical resection should be the first consideration, using preoperative portal vein embolization if needed for hepatic hypertrophy. Patients not amenable to resection can be considered for hepatic arterial therapy with either yttrium-90 microspheres (radioembolization) or chemotherapy (chemoembolization) (Fig. 2). Several local therapies can also be used alone or in combination in the treatment of unresectable peripheral cholangiocarcinoma, including percutaneous seed brachytherapy, stereotactic radiotherapy, and thermal and IRE ablation.

Conclusion
The treatment of cholangiocarcinoma remains a challenge due to relative chemoresistance, frequent non-resectability and high recurrence rates. Systemic treatments, while not covered in this review, are slowly expanding and clearly will play an increased role in the adjuvant, neoadjuvant and recurrent tumor scenarios. Comprehensive treatment paradigms must now consider a wide range of modalities, including resection, radiotherapy, ablation and even transplantation. As in many other tumor types, the establishment of multidisciplinary and multimodal treatment groups is critical not only to the treatment of individual patients, but also to the continued evolution and refinement of practice patterns. Locoregional treatments developed for far more common hepatic tumors such as hepatocellular carcinoma and metastatic colorectal cancer are also finding application for the treatment of cholangiocarcinoma.

References

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solid cancers (e.g., breast, lung, colon), suggesting that there might be a common mechanism conferring aggressive cancer behavior across cancer types.

One of the common features in solid cancers is that tumor cells are surrounded by their host tissue stroma, which mainly consists of extracellular matrix, fibroblasts, blood vessels and immune cells that provide a fertile environment for cancer growth. We found that the majority of our biomarkers of poor survival are not expressed in tumor cells but in the stromal cells and extracellular matrix (Fig. 1). The majority of the 10 genes are known to be involved in collagen cross-linking and their expression is regulated by TGFβ1 signaling, suggesting that TGFβ1-regulated collagen cross-linking might be a common biological process that contributes to poor overall survival.

Notably, inhibition of these genes by genetic or pharmaceutical approaches has been successful in impeding tumor progression in several cancer models, suggesting that collagen cross-linking might be a promising therapeutic target.

Our current research efforts include: (1) optimization and validation of the biomarker panel in a large patient cohort for translation into a clinically applicable assay, (2) determination of the molecular mechanisms by which the 10 biomarker genes contribute to metastasis and chemoresistance, and (3) identification and validation of the key therapeutic targets in patients who express the 10 biomarker genes.

A better understanding of how the collagen-rich stroma drives ovarian cancer progression could reveal the “Achilles’ heel” of the tumor and lead to the development of novel therapeutic strategies.

References
The Next Generation in Molecular Cancer Testing

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As in traditional sequencing, next generation sequencing (NGS) determines the order of nucleotides in the DNA to identify mutations, but does so for many targets simultaneously in a massively parallel manner. Last October, Cedars-Sinai introduced the Cancer Mutation Panel for Personalized Medicine, joining a select group of academic centers now offering this service.

The new assay targets over 2,800 cancer-related mutations in 50 cancer genes using DNA from formalin-fixed, paraffin-embedded patient tissues. This technology is clinically applicable for end-stage disease and clinical trials selection as well as for cancers that are rare, unusually aggressive, atypical in their presentation, refractory to treatment, present in young patients and/or advanced without a known primary.

The test essentially creates a genetic fingerprint of the cancer by simultaneously scanning for multiple mutations in a single assay to identify tumors that are likely to respond to existing or developing targeted therapies, including FDA-approved drugs. To date, we have evaluated tumor samples from lung, prostate, breast, ovary, endometrium, pleural fluid, pancreas, thymus and soft tissue sources. Actionable mutations have been detected across 13 different genes on the panel. The assay has also detected low-frequency mutations and multiple alterations within a single case.

By providing genetically based evidence to tailor treatments, we anticipate this test will have an increasing role in clinical decision-making. Accordingly, Cedars-Sinai has formed a multidisciplinary Molecular Tumor Board to integrate genomic results and clinical information with the goal of guiding therapy selection, decreasing adverse drug events and producing the best possible patient outcomes.

Figure 1: The 50 cancer genes, including both oncogenes and tumor suppressor genes, in the Cancer Mutation Panel for Personalized Medicine. The assay includes coverage of 2,855 hotspot mutations recorded in the Catalog of Somatic Mutations in Cancer (COSMIC).

Selected Cancer Clinical Trials Now Enrolling at Cedars-Sinai

- Immunological targeting of CD-133 in recurrent glioblastoma: a translational and clinical study of an autologous CD-133 DC vaccine (IRB#30646)
- VRXP-A202: Randomized, double blind, placebo controlled study of chemotherapy plus cetuximab in combination with VTX-2337 in patients with recurrent or metastatic squamous cell carcinoma of the head and neck (IRB#33319)
- 2012-002: A phase I/II study of weekly carfilzomib in combination with dexamethasone in progressive multiple myeloma (IRB#33794)
- RTOG 1115: Phase III trial of dose-escalated radiation therapy and standard androgen deprivation therapy with a GnRH agonist vs. dose-escalated radiation therapy and enhanced ADT with a GnRH agonist and TAK-700 for men with high risk prostate cancer (IRB#28908)
- Phase 1 study of veliparib (ABT-888) in combination with gemcitabine and intensity-modulated radiation therapy in patients with locally advanced, unresectable pancreatic cancer (IRB#25528)

For more information about the over 100 cancer clinical trials at Cedars-Sinai, please contact Jaime Richardson, Cancer Clinical Trial Navigator, at 310-423-2133 or Cancer.Trial.Info@cshs.org.