The Future of Biomarkers in Interventional Oncology

Personalized therapies targeting specific biomarkers and cancer genomics are bringing new hope in the management of cancer.

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The lifetime probability that an individual will develop cancer is approximately 40%.[1] Early detection of cancer through developments in medical imaging and advances in systemic and locoregional therapies have resulted in a 23% decline in cancer-related deaths in the United States over the last 25 years.[1]

Nonetheless, ongoing cancer research has ascertained that it is a diverse amalgam of diseases caused by acquired genetic, epigenetic, and genomic alterations in cells in a process that allows the development of abnormal cells. These cells can undergo the six hallmarks of cancer (resisting cell death, sustained proliferation, evading growth suppressors, inducing angiogenesis, cellular immortality, and invasion).[2,3] Standard-of-care therapies have been established through clinical trials and have shown oncologic benefits of new treatment regimens. Despite the contribution of chemotherapy, this approach is suboptimal and does not take into account new knowledge, treating cancer with a one-size-fits-all approach. The development of targeted therapies that profile specific cellular expression of biomarkers, such as individual tumor DNA, RNA, or protein, has changed the outlook on cancer care and has introduced the possibilities of personalized therapies and customized treatment based on specific tumor identity.

The development and evolution of interventional oncology (IO) as a subspecialty of interventional radiology that is dedicated to the care of cancer patients cannot continue without an understanding and utilization of biomarkers and genomics, not only as predictors of oncologic outcomes, but also as important factors that may dictate certain technical and therapeutic modifications.

We would like to highlight some important, clinically validated biomarkers present in diseases we commonly treat, such as hepatocellular carcinoma (HCC), colon cancer liver metastases (CLMs), and non–small cell lung cancer (NSCLC). We believe that knowledge of these biomarkers and what they represent will be imperative to the successful management of patient care by interventional oncologists in the near future.

BIOMARKERS

An ideal biomarker in oncology allows early disease detection while contributing to the patient's prognosis and response to a specific therapy in a relatively inexpensive and reproducible manner. The evaluation of molecular biomarkers is now part of the routine clinical workup and significantly contributes to the decision-making process in the management of prevalent malignant diseases including breast, colorectal, and lung cancers. Pharmaceuticals have been developed to target tumors with certain aberrant genetics. For example, the monoclonal antibody (mAb) trastuzumab targets the human epidermal growth factor receptor 2–positive breast cancer, cetuximab and panitumumab are tyrosine kinase inhibitors used in mutant epidermal growth factor receptor (EGFR) in colon cancer, and erlotinib is an EGFR inhibitor for EGFR-mutant NSCLC. These targeted therapies have improved overall survival for selected patients with specific tumor biology.[4-9] Given the cost and the side effects of these drugs, the utilization of biomarkers to appropriately select patients who will benefit from targeted therapies is imperative.[10]

HEPATIC TUMOR–DIRECTED THERAPIES

Colorectal cancer (CRC) is the third most common cancer worldwide and results in nearly 700,000 deaths per year.[11] Hepatic metastasis is the cause of approximately two-thirds of CRC-related deaths.[12,13]

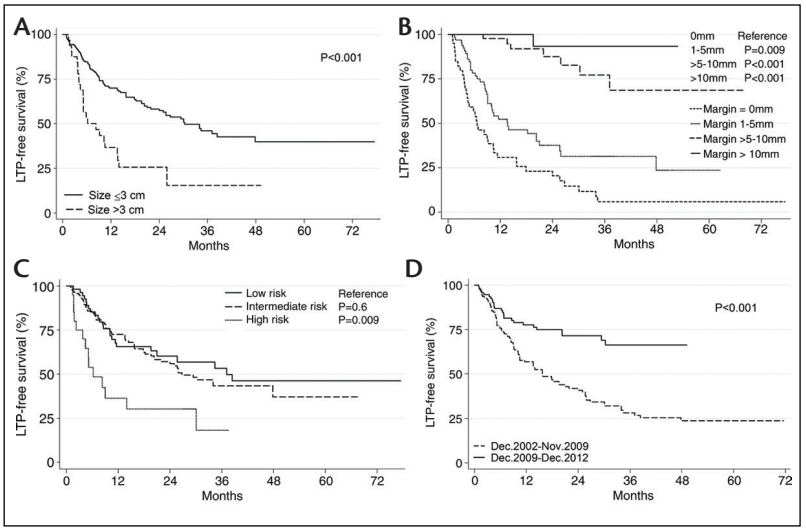

Figure 1. Kaplan-Meier LTPFS (A) and cumulative incidence curves by *KRAS* mutation within ablation margin categories. Reprinted with permission from Shady W, Petre EN, Gonen M, et al. Percutaneous radiofrequency ablation of colorectal cancer liver metastases: factors affecting outcomes—a 10-year experience at a single center. Radiology. 2016;278:601–611.

The development of targeted therapies for particular biomarkers has significantly improved survival for a substantial population of CRC patients who were chemorefractory to standard chemotherapy regimens. EGFR is a transmembrane receptor and member of the ErbB/HER family of tyrosine kinase receptors. It influences two main downstream signaling pathways: the Ras-Raf mitogen-activated protein kinase (MAPK) pathway, which is involved in proliferation of the cell, and the phosphatidylinositol 3-kinase (PI3K)-PTEN-AKT pathway, which is involved in cell survival and motility.[14] Patients with *KRAS* mutations of codons 12 and 13 are resistant to anti-EGFR mAbs, cetuximab, and panitumumab, and this mutation is associated with diminished survival when compared to patients with wild-type *KRAS* CRC.[15,16]

The targeting of these genetic changes is not always straightforward. *BRAF* V600E is a prognostic indicator in CRC. Inhibition of *BRAF* V600E with vemurafenib is an effective treatment for melanoma; however, CRC patients with this mutation typically do not respond to this directed therapy.[17,18] An alternate feedback mechanism from EGFR was identified exclusively in CRC. Tandem blockade of this EGFR feedback pathway along with vemurafenib therapy results in an exceptional treatment response in CRC patients when compared to single-therapy vemurafenib.[19]

To understand the impact of biomarkers on image-guided interventional therapies, various factors have been evaluated that may predict posttreatment outcomes in certain cancers. A recent study evaluated *KRAS* mutations of codons 2, 12, and 13 in patients with CRC liver metastases undergoing percutaneous radiofrequency ablation. *KRAS* mutation was a significant predictor of the development of new liver metastases and diminished overall survival. Perhaps a more important finding was the fact that *KRAS* mutation was a risk factor for local tumor progression (LTP) and ablation failure, particularly in tumors that were ablated with a postablation minimal margin < 6 mm (Figure 1). The LTP rate for a *KRAS* mutant tumor with a minimal margin < 6 mm was 80% compared to 43% for the wild-type tumors ablated with the same size margin.[20]

Postablation minimal margin size is a well-established parameter for determining local tumor control.[21-23] Two-year local tumor progression-free survival (LTPFS) for CLMs ablated with minimal margins of 0, 1 to 5 mm, 6 to 10 mm, and 11 to 15 mm were 26%, 46%, 74%, and 80%, respectively.[24] Evaluating tissue adherent to the radiofrequency ablation electrode after ablation indicated that the presence of residual tumor cells expressing the proliferation marker Ki-67 carried a significantly increased risk of LTP and diminished overall survival after liver tumor radiofrequency ablation (Figures 2 and 3).[25,26] A prospective, single-center study evaluated biopsies and margin of the ablation zone immediately after radiofrequency ablation and assessed whether the presence of viable (oxPhos antibody) or prolific (Ki-67) tumor cells was a strong predictor of oncologic outcomes. Multivariate analysis indicated that a margin size < 5 mm, tumor size > 3 cm, and the presence of viable/prolific tumor cells from the ablation zone were significant independent predictors of LTP.[21] At 1 year, only 3% of patients with tumor-negative biopsy and margin size of at least 5 mm had LTP.[27] On the contrary, tumor viability (Ki-67 positivity) combined with margins < 5 mm carried a 23 times higher risk for LTP and a 1-year LTP of 73%.[21]

Biomarkers have also been studied in transcatheter arterial-directed treatments in the liver. Nucleosomes and biochemical markers measured from the serum, as well as carcinoembryonic antigen, cancer antigen 19-9, CYFRA 21-1, C-reactive protein, lactate dehydrogenase, aspartate aminotransferase, choline esterase, gamma-glutamyl transferase, alkaline phosphatase, and amylase were found to be prognostic indicators for overall survival in patients undergoing yttrium-90 radioembolization

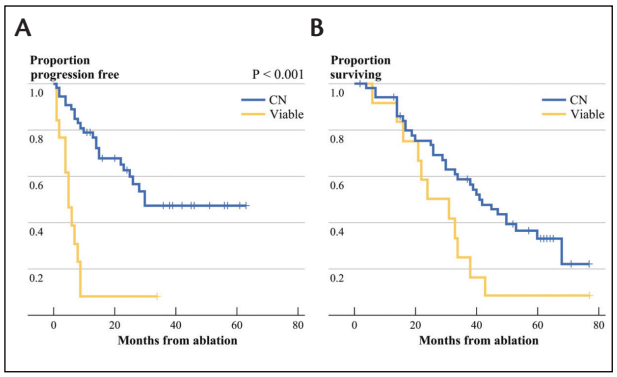

Figure 2. Kaplan-Meier curves of LTPFS and overall survival in coagulation necrosis (CN) and viable tumor groups. Reprinted from Sofocleous CT, Garg S, Petrovic LM, et al. Ki-67 is a prognostic biomarker of survival after radiofrequency ablation of liver malignancies. Ann Surg Oncol. 2012;19:4262–4269, with permission of Springer.

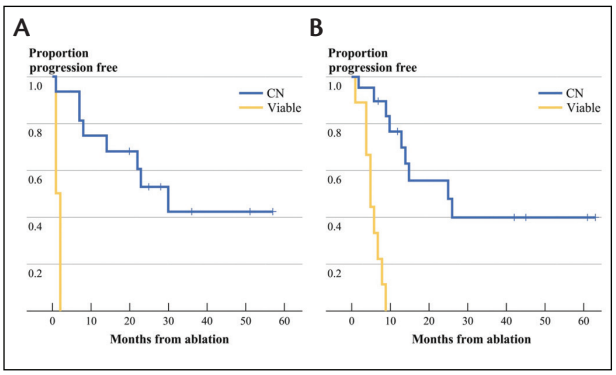

Figure 3. LTPFS for HCC lesions (A) or CRC lesions (B) based on whether tissue was viable tumor or coagulation necrosis (CN) status. Reprinted from Sofocleous CT, Garg S, Petrovic LM, et al. Ki-67 is a prognostic biomarker of survival after radiofrequency ablation of liver malignancies. Ann Surg Oncol. 2012;19:4262–4269, with permission of Springer.

for CLMs.[28] Measurements of immunogenic cell markers high-mobility group box 1 (HMGB1), RAGE (receptors of advanced glycation end products), and DNAse from the serum found that HMGB1 levels were significantly higher in patients who progressed after transarterial radioembolization (TARE) for CLMs, and it was an independent prognostic indicator for survival.[29] The presence of a mutated PI3K was also a significant predictor of LTP after TARE for CLMs when compared to wild-type PI3K.[30]

Predictors of outcomes for HCC after IO therapies have been identified within the serum. Alpha-fetoprotein (AFP), des-gamma-carboxy prothrombin (DLP), and lens culinaris agglutinin-reactive fraction of alpha-fetoprotein (AFP-L3) are potentially useful biomarkers after transcatheter therapy.[31,32] The genetic expression of chemotherapy sensitivity, hypoxia, mitosis, and inflammatory genes were analyzed in biospecimens obtained before and after treatment of HCC. Patients with complete response had significantly higher mRNA expression of ATF4, BAX, CCNE, KIF11, NFX1, PPP3CA, SNX1, TOP2A, and TOP2B when compared to partial responders.[33]

A study of serum microRNA-34a and AFP after radiofrequency ablation in HCC established that low levels of miR-34a and high AFP are independent predictors of recurrence.[34] Ki-67 and p130 expression are also negatively correlated with successful transcatheter treatment. Surrogate cross-sectional imaging biomarkers such as diffusion-weighted imaging, perfusion imaging, and dual-phase cone-beam CT have also shown promise in evaluating outcomes post-IO therapy in the setting of HCC.[35]

Biomarkers have also been shown to have benefits in evaluating non-IO liver-directed therapies. CRC patients with the wild-type *KRAS* had better overall survival when FOLFIRI was combined with cetuximab.[16] The p53, Ki-67, thymidylate synthase, and human telomerase reverse transcriptase biomarkers have been identified as predictive of outcomes after surgical resection in CRC.[36]

LUNG CANCER

NSCLC is the leading cause of cancer-related deaths in the United States, accounting for more than a quarter of all mortalities.[1] A platinum-based doublet therapy is the standard of care for locally advanced or advanced NSCLC, with poor outcomes and 5-year survival of < 5%.[37] The use of aberrant biomarkers through the application of molecular inhibitors has been implemented in treatment.

Gefitinib, erlotinib, or afatinib, which are small molecules that target EGFR, are now first-line therapy for NSCLC patients with EGFR mutation.[38,39] In patients with an anaplastic lymphoma kinase (ALK) gene rearrangement, the recommended first-line therapy is crizotinib.[38,39] Crizotinib can be first-line or salvage therapy for patients with a mutation in the ROS1 proto-oncogene receptor tyrosine kinase.[38,39] These targeted therapies have added survival benefits for patients when compared to standard-of-care therapies; however, prolonged disease control and survival outcomes remain limited.[40-42] Unfortunately, only about 10% to 15% of patients have EGFR mutations and 2% to 7% have ALK rearrangements.[43,44]

In percutaneous IO therapy, the presence of Ki-67 positivity postablation was an independent risk factor of LTP and shorter LTPFS in NSCLC,[45-47] as well as shorted disease-specific survival for patients who underwent ablation for lung tumors.[45] Similarly, the *KRAS* muta-

tion had an impact on patients after lung tumor ablation. Recurrence rates at 1 and 3 years for *KRAS* mutant tumors were 40% and 63% compared to 20% and 35% for *KRAS* wild-type tumors.[48]

CONCLUSION

IO is rapidly evolving and is considered one of the four pillars of oncology along with surgical, medical, and radiation oncology. A cancer cure cannot be achieved with the use of cytotoxic agents alone. Personalized therapies targeting specific biomarkers and cancer genomics have brought about a new hope and dynamic in the management of cancer. The development and application of biomarkers in IO is a rapidly growing field with an incredible amount of cross-talk between different malignancies, including CRC, NSCLC, breast cancer, and HCC. Several influential biomarkers have been identified, defining IO treatment success. Continued investigation and application of biomarker information in daily IO practice are essential. Further evolution of personalized medicine and use of genomic information in all pillars of oncology will improve oncologic outcomes and carries the hope of cancer eradication. ■

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Disclosures: None.