Revolutionizing Cancer Treatment: Harnessing the Power of Biomarkers to Improve Patient Outcomes

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Abstract

There has been an increasing number of approvals for targeted therapies and immunotherapies in oncology in the past decade. This has changed the treatment paradigm for many solid tumors and hematologic malignancies, and therefore the outcomes of patients with cancer. Advanced practitioners should be up to date with advances in cancer biomarker testing and its implications for the use of targeted therapy and immunotherapy to integrate this information into clinical decision-making.

Over the past decade, an increasing number of targeted cancer therapies and immunotherapies have been approved by the US Food and Drug Administration (FDA) for a broad range of solid tumors and hematologic malignancies. While all of these treatments are designed to induce apoptosis or inhibit tumor growth, they rely on diverse mechanisms of action. Examples include tyrosine kinase inhibitors, monoclonal antibodies directed against tumor antigens, and immune checkpoint inhibitors (ICIs). Such precision medicine has changed the treatment paradigm for many advanced cancers and has begun to be used more often in earlier-stage disease. This evolution has been accompanied by rapid growth in the number and variety of methods used to characterize targetable alterations in tumor cells, i.e., biomarkers. The goal of biomarker-directed precision medicine is to more accurately predict which therapies will result in improved outcomes for a given group of patients based on their tumors' genomic and/or immune marker profile (Saadeh et al., 2019).

While much research has focused on the characterization of prognostic biomarkers to assess the risk of disease recurrence and death, this information may not inform decision-making. In contrast, predictive biomarkers can help identify patients who are more likely to benefit from targeted therapy

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or immunotherapy based on alterations in genomic profile or tumor expression of target proteins, and such results can aid in treatment decisions. Germline genetic alterations such as *BRCA1/2* mutations can also guide the use of agents such as PARP inhibitors for certain malignancies.

BENEFITS OF BIOMARKER-TARGETED THERAPY

Many studies have clearly demonstrated the benefits of biomarker testing for cancer therapy. In patients with non–small cell lung cancer (NSCLC) who have a targetable alteration as determined by comprehensive genomic profiling, use of a National Comprehensive Cancer Network (NCCN) Guideline–recommended targeted therapy resulted in a significantly longer overall survival compared with an alternative therapy (18.6 months vs. 11.4 months; Singal et al., 2019). Similarly, a comprehensive genomic profiling study in patients with recurrent endometrial cancer classified tumors according to molecular subtype to identify relevant targetable genetic alterations. More than 30% of these patients were able to receive a targeted therapy matched to their tumor profile, resulting in a 25% objective response rate and an additional 37% with stable disease (Prendergast et al., 2019). Biomarker testing can thus aid in personalizing cancer therapy for individual patients, ideally improving outcomes and reducing unnecessary toxicity. The use of molecular testing and targeted therapy, where indicated, is now considered the standard of care for many solid tumors, including lung, breast, and gastrointestinal malignancies, and for some leukemias and lymphomas.

The expression of predictive biomarkers has long been used to identify patients who are eligible for hormone therapy. Tumor expression of estrogen and progesterone receptors (ER/PR+), for example, indicates which patients with breast cancer are candidates for hormone therapy such as tamoxifen and aromatase inhibitors. Newer therapies targeting aberrantly expressed protein biomarkers now provide greater tumor cell specificity in breast cancer and other malignancies.

RISE OF TARGETED AGENTS

One of the first oncologic targeted agents developed was trastuzumab (Herceptin) for the treatment of HER2-positive breast cancer. This was based on the discovery that the *HER2* oncogene is overexpressed in selected breast cancers, and that a therapeutic HER2-directed monoclonal antibody such as trastuzumab could inhibit tumor growth when used alone or in combination with chemotherapy (Cobleigh et al., 1999; Slamon et al., 2001). Trastuzumab was the first nonhormonal targeted therapy to require biomarker testing to measure HER2 expression and thus the suitability of this therapy for patients with HER2-overexpressing metastatic breast cancer. Subsequently, additional HER2-targeted agents like lapatinib (Tykerb) and trastuzumab emtansine (Kadcyla) were developed for breast cancer and other tumors that overexpress HER2.

The BCR-ABL tyrosine kinase inhibitor imatinib (Gleevec), which was the first targeted agent for hematologic malignancies, was approved for patients with chronic myeloid leukemia bearing the Philadelphia chromosome biomarker (Ph+ CML; Cohen et al., 2002).

Clinical development of gefitinib (Iressa), an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, highlighted the need to select the appropriate target patient population when considering molecular-based therapy. Early trials of this agent in unselected patients with advanced NSCLC showed little efficacy, while later studies found higher response rates in certain patient subgroups (Asians and never-smokers) with a higher incidence of *EGFR* mutations (Armour & Watkins, 2010). Subsequent clinical trials like IPASS indicated that the presence of an *EGFR* mutation was the strongest predictor of improved progression-free survival and overall response rate with gefitinib compared with carboplatin/paclitaxel as first-line therapy for advanced NSCLC (Mok et al., 2009). Gefitinib was subsequently approved as first-line treatment of metastatic NSCLC bearing specific *EGFR* mutations as detected by an FDA-approved test. These data emphasized the importance of biomarker testing to confirm the presence of specific target mutations and ensure effective use of this EGFR inhibitor.

Similar results have also been seen with other targeted anticancer drugs for which specific biomarker-selected populations exhibit a greater response to therapy compared with nonselected

or wild-type patients (Hoy, 2020; Larkins et al., 2016; Marcus et al., 2021; Mathieu et al., 2022). The clinical use of ICIs has also rapidly expanded following initial trials that demonstrated the efficacy of the CTLA-4 inhibitor ipilimumab (Yervoy) in metastatic melanoma (Lipson & Drake, 2011). Subsequent studies found that other ICIs, such as pembrolizumab (Keytruda) and nivolumab (Opdivo), were active against melanoma and other selected solid tumors (Lee et al., 2022).

Since the initial approval of nivolumab for NSCLC in 2015, many additional ICIs have been approved. For some ICIs, biomarker expression of the PD-L1 target protein is required for the treatment of certain tumors. These discoveries, as well as changes in oncoprotein expression and immune checkpoints seen in some tumors, have spurred the development of numerous cancer therapies specifically targeted to biomarker-identified alterations.

Early efforts at genomic sequencing by the Human Genome Project (Wilson & Nicholls, 2015) and The Cancer Genome Atlas (Cancer Genome Atlas Research Network et al., 2013), coupled with later technological advances in sequencing (next-generation and whole genome and exome sequencing) and data analysis, led to the identification of many other genetic alterations in tumors, some of which are related to tumor growth and metastasis. Continued research will undoubtedly help identify additional targetable alterations and facilitate the development of new molecular targeted agents. The need to identify and clinically evaluate new and better predictive biomarkers that can be used for patient selection of appropriate cancer therapy will therefore continue to grow.

TUMOR-AGNOSTIC THERAPIES

Several precision medicine therapies have been approved for use in a variety of tumors, rather than being limited to a single indication. These agents are designed to target biomarkers expressed in multiple tumor types, regardless of their location or histology. To date, seven tumor-agnostic therapies have been approved, including two used in combination (dabrafenib [Tafinlar] and trametinib [Mekinist]). For example, although the frequency of microsatellite instability-high (MSI-H) varies widely among tumor types, ICI therapy often results in high response rates and improved survival in patients with MSI-H tumors (Danesi et al., 2021). The challenge going forward will be to identify better predictive biomarkers that can refine patient selection for tumor-agnostic therapies and further improve outcomes. Additionally, it is not always clear what biomarker assay to use in these circumstances. The FDA approved pembrolizumab for use in patients with MSI-H/mismatch repair deficient (dMMR) unresectable solid tumors or high tumor mutational burden but did not indicate a preferred method for determining MSI/MMR status (Jørgensen, 2020). The optimal approach (e.g., immunohistochemistry, next-generation sequencing, or tumor mutational burden) may depend on the type of malignancy under consideration (Bartley et al., 2022).

Ongoing studies using novel clinical trial designs are also attempting to further identify targetable tumor alterations, particularly in patients with refractory or rare malignancies, as discussed in detail in an accompanying article in this supplement. NCI-MATCH is a large phase II precision medicine trial that aims to guide the selection of appropriate targeted therapy for patients with advanced, refractory malignancies based on the presence of genetic abnormalities, rather than selecting treatment according to tumor type. Specific genetic biomarkers such as mutations, gene amplification, and dMMR are identified, with treatments assigned based on genomic profiles. NCI-MATCH thus seeks to maximize the clinical benefits of molecular precision therapy by first determining the presence of actionable mutations that could be candidates for targeted therapy, regardless of tumor type (Murciano-Goroff et al., 2021).

The trial has already demonstrated the feasibility of detecting rare alterations, and in some cases has proven the benefits of this approach. The robust accrual rate highlights the unmet need for access to novel therapies, with approximately two thirds of patients enrolling through community oncology practices. The phase II TAPUR Study is evaluating molecular-based therapy across multiple tumor types in patients bearing a molecular alteration that can be targeted by an approved agent (Mangat et al., 2018). This approach also provides an opportunity to identify potential additional new uses of these agents in nonapproved tumor types.

RESOURCES FOR APs AND PATIENTS

This supplement to the *Journal of the Advanced Practitioner in Oncology* (JADPRO) is intended to provide advanced practitioners with practical information and resources on cancer biomarker testing and its implications for use of targeted therapy and immunotherapy. We have attempted to provide an in-depth review of cancer biomarkers, including testing methodology, actionable recommended therapies based on biomarker status for selected solid tumors and hematologic malignancies, and use of tumor-agnostic therapies. We also outline the roles advanced practitioners play in biomarker testing and highlight how they can help integrate this information into clinical decision-making.

Accompanying this supplement is a patient education guide that details a patient's experience with biomarker testing, suggests questions to ask their treatment team, and provides a list of online patient resources. Advanced practitioners can request extra complimentary copies of the print guide to distribute to patients and/or share the digital version found at patiented.jadpro.com/biomarker. Patients may also benefit from an interactive education video activity called "Biomarker Testing in Cancer: Empowering Patients for Important Discussions With the Care Team" that was created to help teach patients about biomarker testing, why it may be needed, and how test results may help their treatment team select the best therapy. Laura Okolo, DNP, MSN, FNP-BC, interviews several colleagues about their roles on the treatment team and how they help guide their patients through the process of biomarker testing. We encourage you to share this resource with your patients and colleagues, which can be found at patiented.jadpro.com/biomarker.

We hope this supplement and the resources provide advanced practitioners—and their patients—with a better understanding of biomarker testing in oncology and how it can inform selection of therapy, as well as practical tools to optimize outcomes.

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